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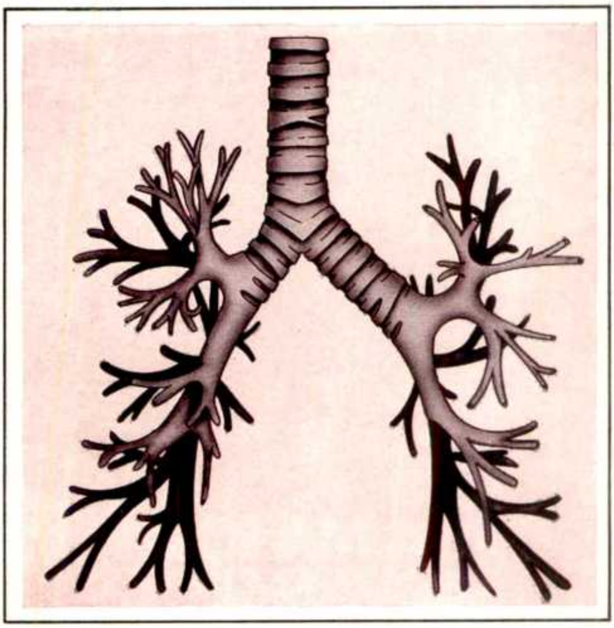

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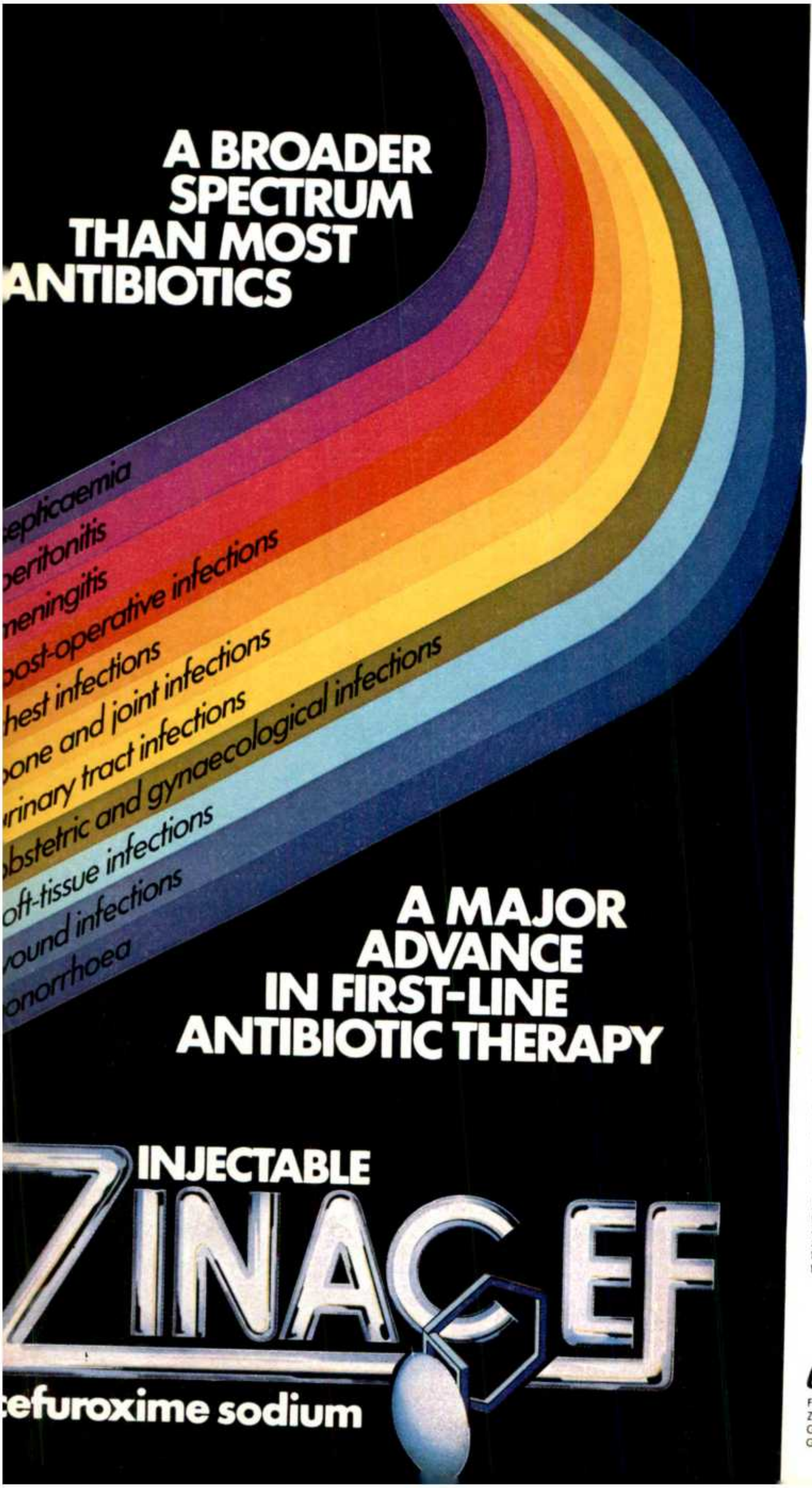

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Br. J. Dis. Chest (1982) *76*, 1

ASBESTOS PLEURAL DISEASE

MARK G. BRITTON

The London Hospital (Whitechapel), London

Summary

The lung function tests on 88 asbestos workers known to have an asbestos-related abnormality on the chest radiograph have been analysed with respect to pleural disease. The degree of intrapulmonary and pleural disease were assessed by reading posteroanterior and both oblique films according to a modified ILO U/C Classification (1971).

The results show a highly significant decrease in lung function with increasing pleural abnormality. Analyses suggest that these changes cannot be wholly accounted for by confounding variables such as airways obstruction and/or pulmonary fibrosis. We conclude that pleural thickening alone, particularly when severe, contributes to the decreased vital capacity and to any resultant disability.

INTRODUCTION

An assessment of the effect of asbestos pleural disease is made difficult by the possible additional presence of pulmonary fibrosis and/or airway obstruction. Harries (1970) noted that men with pleural abnormality had more symptoms and lower lung function values than men without pleural abnormality. Lumley (1977) showed significant impairment in submaximal exercise testing in men with diffuse pleural thickening.

However, controversy remains as to whether pleural thickening can occur alone without any associated intrapulmonary fibrosis and whether it can give rise to disability. We have reviewed the results obtained from a group of asbestos workers in an attempt to answer these questions.

Patients and Methods

One hundred asbestos workers were included in the study. Approximately half had been referred for lung function testing as part of an assessment relating to claims for compensation; the remainder were under the care of The London Hospital or the East Ham Asbestos Clinic. All the men were seen at the London Hospital between August 1976 and August 1977, and all had a detectable abnormality on their chest radiograph which was thought to be related to their previous asbestos exposure. The various manifestations which can result from exposure to asbestos, including the pleural changes are listed in Table I.

A medical history, including full details of present and past occupation, was followed by clinical examination. Lung function tests included simple spirometry, measurement of lung volumes, rebreathing $P\text{CO}_2$ and transfer factor by the methods described by Hughes and Empey (1972) and the predicted values were those of Cotes (1975).

Posteroanterior, lateral and right and left oblique chest radiographs were read 'blindly' by the author and were classified according to a modified form of the ILO U/C International Classification (1971) by comparison with standard films. The modifications included an assessment of

Table I. Manifestations of asbestos exposure

1. Asbestos bodies
2. Asbestos pleural changes
    - (*a*) Plaque formation
        - (*i*) Hyaline
        - (*ii*) Calcified
    - (*b*) Pleuritic reaction (pleuritis)
        - (*i*) Pleural effusion (acute)
        - (*ii*) Pleural thickening (chronic)
3. Asbestosis (pulmonary fibrosis)
4. Asbestos granuloma (asbestoma)
5. Carcinoma
    - (*a*) Bronchus
    - (*b*) ? Larynx and others
6. Mesothelioma
    - (*a*) Pleural
    - (*b*) Peritoneal

pleural disease for each side separately, and the use of the oblique films in conjunction with the posteroanterior film, allowed a more accurate measurement of the width (thickness) and extent of the disease anteriorly and posteriorly. The author's ability to use the ILO U/C Classification has been verified by comparing his readings of 100 standard films with those of 15 expert readers.

The ILO U/C Classification 1971 does not allow a clear distinction to be made between plaques and diffuse pleural thickening. In our study both types of pleural disease were assessed together under the heading of pleural thickening, but, a note was made of which type was predominant, according to the criteria of Sheers and Templeton (1968) for differentiation between the two types.

The pleural disease was assessed by grading the width, extent, and involvement of the costophrenic angles for each side separately as follows:

	ILO U/C Grading	Numerical Code
Width	a b c	0–3
Extent	0 1 2	0–2
Costophrenic angle	No/Yes	0–1

A numerical grading for expressing the extent of pleural disease was calculated for each subject by multiplying the 'extent' and 'width' of the pleural disease for each side separately, and adding each side's score together with the values for the costophrenic angles if these were involved, thus giving a possible score from 0 to 14. The subjects were then divided into five groups (Groups I-V) according to their scores.

Pleural calcification was graded on an 0–3 scale for each of the possible five sites of calcification, namely right and left chest walls, right and left diaphragms and 'other' sites. A score was calculated by addition giving a possible range from 0 to 15 and the subjects were then divided into three groups (Group A, B and C) according to their scores.

The means, standard deviations and standard error of the means were calculated for each group and the differences between the group means were identified using a one-way analysis of variance. Trends across the five pleural groups (I-V) and the three calcification groups (A, B and C) were assessed using a linear term in the analysis of variance and confirmed by the Spearman rank correlation coefficient using the actual scores rather than the groupings. In studying the joint effect of pleural and pulmonary disease a two-way analysis of variance was computed. Significance levels are quoted for the effect of the two conditions and where there is an interaction between them. If the interaction is significant the effect of the pleural disease is then dependent on the amount of pulmonary disease.

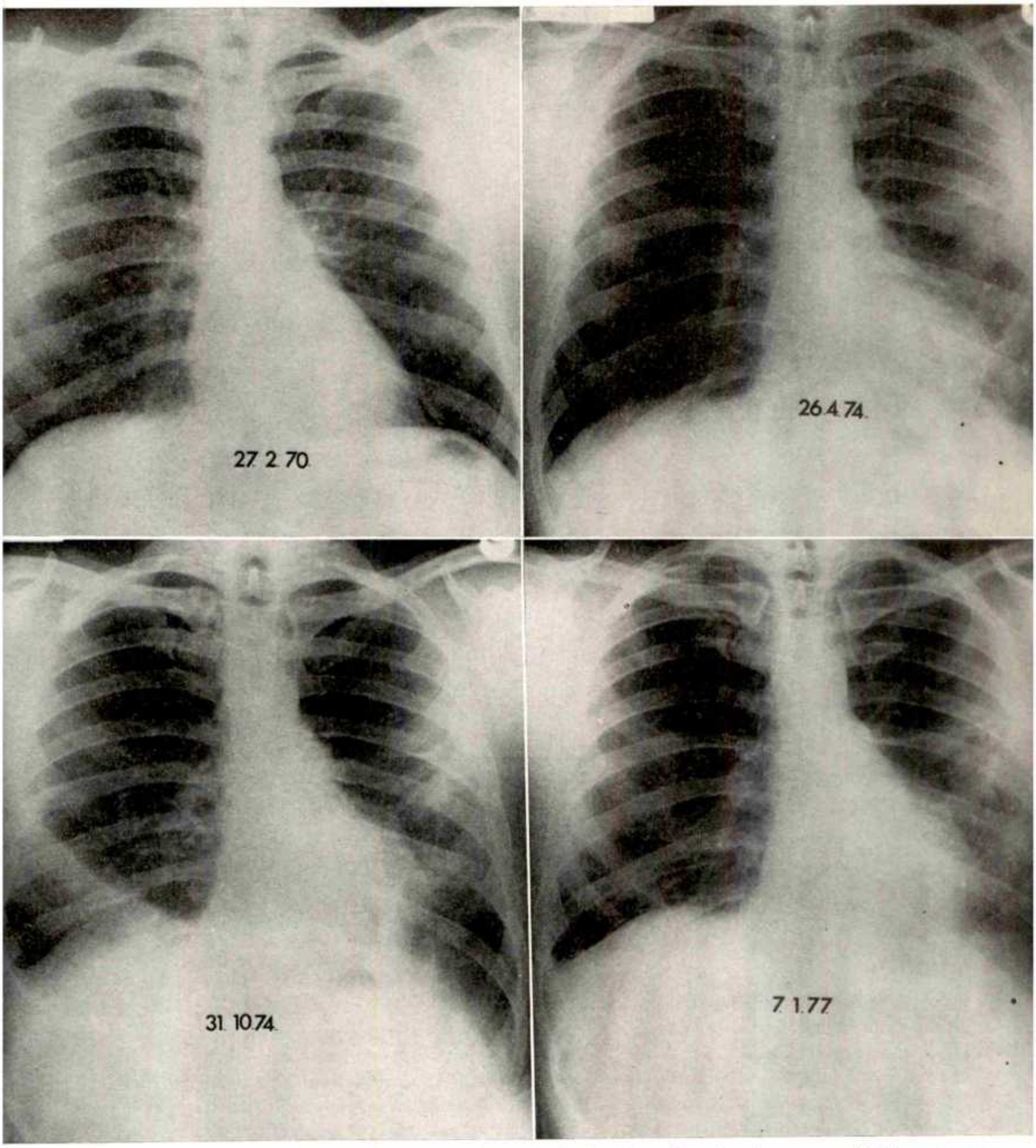

Fig. 1. Serial radiographs of the patient described, showing the development of bilateral acute pleural reactions and resultant pleural thickening

RESULTS

There were 93 males and seven females ranging in age from 32 to 83 with a mean of 56.6 ± 8.9 years.

Twelve subjects have been excluded from this study because of other chest conditions which would have affected their lung function. The reasons for exclusion included carcinoma of the lung, mesothelioma, emphysema, tuberculosis, bronchiectasis, severe ankylosing spondylitis and previous thoracic surgery.

The case history of one subject, a 34-year-old lagger, with details of serial lung function and serial radiographs illustrates the possible sequential changes in the development of diffuse pleural thickening.

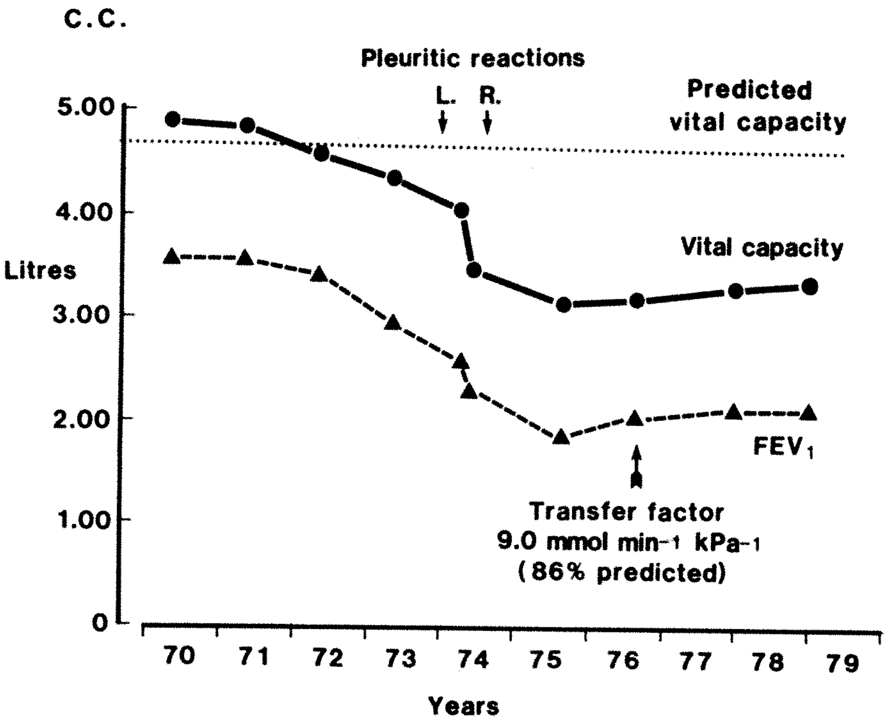

Fig. 2. Serial lung function tests on the patient described in relation to the bilateral acute pleuritic reactions

Case history

The patient had been a lagger since leaving school at the age of 15 in 1960 and had been a life-long non-smoker. He had been under yearly follow-up at a chest clinic since 1970. In April 1974 he was asymptomatic, but three months previously had experienced mild left pleuritic pain which had lasted for approximately two weeks. His radiograph at this time showed a left pleural reaction with a small basal effusion. Six months later and without intervention the radiograph showed partial resolution of the changes on the left but a similar pleural reaction and effusion on the right. A later radiograph showed considerable residual pleural thickening which is shown more clearly on the computerized tomograms of the chest (Fig. 3). Serial lung function tests at various stages of his illness are shown in Fig. 2.

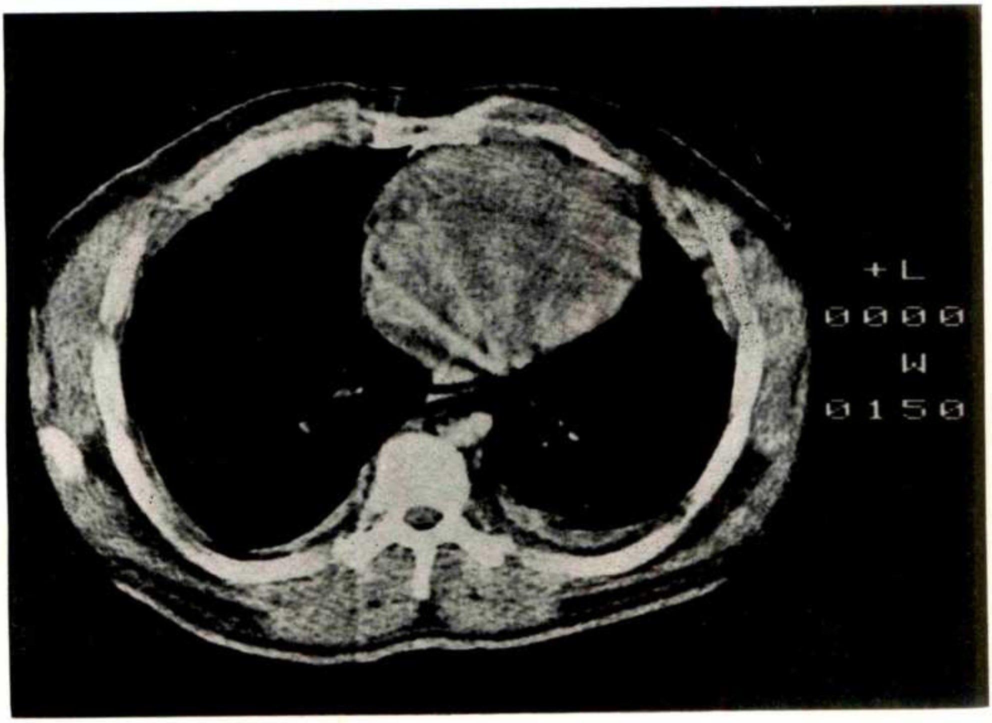

Fig. 3. A CAT scan (1978) of the patient described, showing bilateral pleural thickening, most marked on the left anterior chest wall

Table II divides the group of 88 workers according to the extent of pleural disease and shows age, exposure to asbestos, and relevant lung function tests. By virtue of the definitions used most of the subjects with plaques alone were either Group II or III and most of Groups IV and V had varying degrees of diffuse pleural thickening.

The results show that the workers in Group V (i.e. with moderate to severe pleural thickening) are slightly younger, but details of exposure for the groups do not differ significantly. There is a statistically significant trend for the vital capacity, expressed as litres ($P < 0.005$) and as a percentage of predicted value ($P < 0.001$), to decrease with increasing pleural score. Neither the transfer factor nor the FEV_1/FVC ratio show any significant trend between the groups. The absolute peak flow values do show a similar decreasing trend but this does not reach statistical significance.

Details of vital capacity and transfer factor (TF), both expressed as a percentage of the predicted value, the FEV_1/FVC ratio and the degree of dyspnoea according to the MRC Questionaire (1966) grading are considered in relation to both extent of pleural disease and degree of pulmonary fibrosis in Table III. These analyses show a significant trend of decrease of vital capacity with increase of pleural score in all three groups with different degrees of pulmonary fibrosis. The values for the FEV_1/FVC ratio do not show a statistically significant trend either within or between the profusion score groups. However in three of the groups FEV_1/FVC ratio is less than 70% and it would appear that this added airway obstruction may influence the vital capacity as seen especially in one group (Group 3, profusion score 1/1-2/3) where the vital capacity would appear

Table II. Details of age, exposure to asbestos, and lung function for the five groups with varying degrees of asbestos pleural disease

Pleural score	*n*	*Age*	*Date of 1st exposure*	*Length of exposure*	*Vital capacity*		FEV$_1$/ FVC (%)	*TF* (% pred.)	*PEFR* (litres/min)
					litres	% pred.			
Group 1:0	9	58.4 (±3.1)	1940 (±4.6)	20.2 (±4.7)	3.85 (±0.38)	92.8 (±6.8)	73.6 (±4.7)	72.0 (±5.8)	450 (±64)
Group II:1 and 2	26	55.2 (±2.2)	1946 (±2.3)	19.2 (±2.6)	3.39 (±0.18)	86.6 (±3.3)	72.5 (±2.0)	71.2 (±4.1)	412 (±25)
Group III:3, 4 and 5	31	55.7 (±1.4)	1943 (±1.7)	25.9 (±2.1)	3.19 (±0.14)	80.2 (±2.6)	68.7 (±2.4)	65.4 (±3.1)	416 (±19)
Group IV:6, 7 and 8	15	58.6 (±1.7)	1946 (±2.6)	18.8 (±4.1)	2.98 (±0.23)	77.4 (±5.2)	73.7 (±3.4)	65.7 (±3.3)	400 (+34)
Group V:9 and above	7	49.0 (±3.5)	1943 (±3.5)	23.3 (±3.6)	2.49 (±0.18)	60.0 (±3.3)	71.3 (±3.7)	73.5 (±6.1)	364 (±42)
Analysis of variance linear term			NS	NS	NS	$P<0.001$	$P<0.001$	NS	NS
Spearman rank correlation			NS	NS	NS	$P<0.005$ ($R=-0.31$)	$P<0.001$ ($R=-0.42$)	NS	NS

(NS = $P>0.05$)

Table III. Details of lung function, and dyspnoea grading with varying degrees of asbestos pleural and pulmonary disease

Pleural score	*Profusion score* 0/0–1/0					*Profusion score* 1/1–2/1					*Profusion score* > 2/2				
	n	VC (% pred.)	TF (% pred.)	FEV_1/FVC (%)	Dyspnoea	*n*	VC (% pred.)	TF (% pred.)	FEV_1/FVC (%)	Dyspnoea	*n*	VC (% pred.)	TF (% pred.)	FEV_1/FVC (%)	Dyspnoea
Group I 0	6	93	75	72.8	1.0	2	92	69	77.6	1.0	1	92	60	75.3	1.0
Group II 1 and 2	15	86	75	73.3	1.8	9	86	69	71.0	2.1	2	90	55	72.5	3.0
Group III 3, 4 and 5	10	88	73	71.4	1.8	10	76	65	66.0	2.2	11	77	60	68.9	2.6
Group IV 6, 7 and 8	4	80	66	72.4	1.5	7	87	75	70.6	2.0	4	60	51	80.3	2.5
Group V 9 and above	3	66	85	70.5	2.0	3	57	70	76.2	2.7	1	48	51	60.6	3.0

Two-way analysis of variance *P* values for:	VC (% pred.)	TF (% pred.)	FEV_1/FVC (%)	Dyspnoea
Effect of pleural score	0.003	0.97	0.68	0.07
Effect of profusion score	0.14	0.007	0.81	0.04
Interaction	0.55	0.87	0.93	0.99

Table IV. Details of age, exposure to asbestos, and lung function for the three groups with different degrees of pleural calcification

Calcification score	*n*	*Age*	*Date of 1st exposure*	*Length of exposure*	VC (% pred.)	TF (% pred.)	*PEFR* (litres/min)
Group A (no calcification): 0	48	52.5 (±1.3)	1948 (±1.3)	18.8 (±1.6)	81.8 (±2.8)	69.2 (±2.5)	435 (±19)
Group B (mild calcification): 1–4	28	58.3 (±1.4)	1943 (±1.9)	23.1 (±2.5)	83.7 (±3.1)	68.5 (±3.3)	390 (±22)
Group C: (moderate/severe calcification): 5 and above	12	63.6 (±1.5)	1932 (±2.6)	31.3 (±5.1)	74.2 (±4.8)	65.9 (±6.3)	370 (±36)
Analysis of variance linear form		$P<0.001$	$P<0.001$	$P<0.001$	NS	NS	$P<0.05$
Spearman rank correlation		$P<0.001$ (R=0.45)	$P<0.001$ (R=0.45)	$P<0.001$ (R=0.28)	NS	NS	$P<0.05$ (R=0.21)

(NS=$P>0.05$)

to be lower than appropriate considering the general trend. There is no significant trend of transfer factor within each profusion score group but changes between the groups show decreasing values with increasing pulmonary fibrosis.

Table IV gives details of age, exposure and lung function for the three groups with different degrees of pleural calcification. There is a downward trend of VC and TF with increasing calcification but this does not reach statistical significance. The workers in Group C, those with moderate/severe calcification, tend to be older and to have been exposed to asbestos earlier in life and for longer.

DISCUSSION

Becklake et al. (1970) reported small but consistent reductions in lung function in asbestos workers with pleural abnormalities, and Harries (1970) showed that men with pleural abnormalities had more symptoms and signs and lower lung function values than those without pleural abnormality, suggesting that some men with extensive pleural fibrosis were dyspnoeic as a result.

However, Jones and Sheers (1973) supported the earlier findings of Leatheart (1968) and stated that localized pleural plaques are not associated with symptoms or abnormal physical signs. In a study of lung function at rest and during progressive submaximal exercise in a group of men with varying degrees of asbestos-related pleural abnormality (Lumley 1977), diffuse pleural thickening and to a lesser extent non-calcified pleural plaques were associated with substantial functional abnormality, but, pleural calcification was not associated with any significant functional impairment.

Our study has shown increasing impairment of lung function with increasing severity of pleural disease irrespective of the degree of pulmonary fibrosis. However, the presence of coexistent airways obstruction, to be expected in a group of industrial workers in this age range, can undoubtedly influence the vital capacity, as shown by one group in particular. The FEV_1/FVC ratios do not show any particular trend with increasing pleural abnormality and although the peak flow values do show a trend, this does not reach significance, so it is unlikely that airways obstruction can account for all the changes seen.

The ILO U/C Classification (1971) was designed for the reading of posteroanterior radiographs alone. The use of oblique views in addition allows a clearer view of pleural changes on the anterior and posterior chest walls, which are only seen 'face-on' in posteroanterior views, thus permitting a more realistic assessment of the total pleural disease present. In this study, oblique films were used and measurements of pleural disease were made for each side independently. Where possible distinction was made between plaques, which are described as being circumscribed, and diffuse pleural thickening.

The accuracy of an assessment of underlying intrapulmonary fibrosis from a radiograph showing extensive pleural disease is questionable and some new method of assessment such as CAT scanning is needed. However, our data suggest that the decrease in vital capacity seen in the few patients with severe pleural disease was not due to fibrosis alone. In the three patients in Group V, in whom a zero profusion score was recorded, the transfer factor was within normal limits. One of the three (the case described) showed no evidence of intrapulmonary disease throughout nine years observation including a CAT scan. The substantial fall in his lung volume occurred at the time of his pleuritic reactions, suggesting cause and effect. This type of patient who has no evidence of intrapulmonary fibrosis does not qualify for compensation by Industrial Injuries Disablement Benefit.

The sequence illustrated by the case history lends support to the theory that an acute pleuritic reaction plus effusion may be the precursor to pleural thickening (Gaensler & Kaplan 1971) and as the reaction may be virtually asymptomatic if the effusion is small, the majority of such episodes probably go undetected.

Despite the difficult problems of apportioning reduction in lung function to airways obstruction, intrapulmonary fibrosis and pleural thickening when all three may occur together, the analyses we present suggest that the trends of reduction in vital capacity with increasing grades of pleural involvement, are unlikely to be wholly the result of airways obstruction and/or intrapulmonary fibrosis. Thus it is concluded that pleural involvement alone, particularly when severe, contributes to a decrease of vital capacity, and to any resultant disability.

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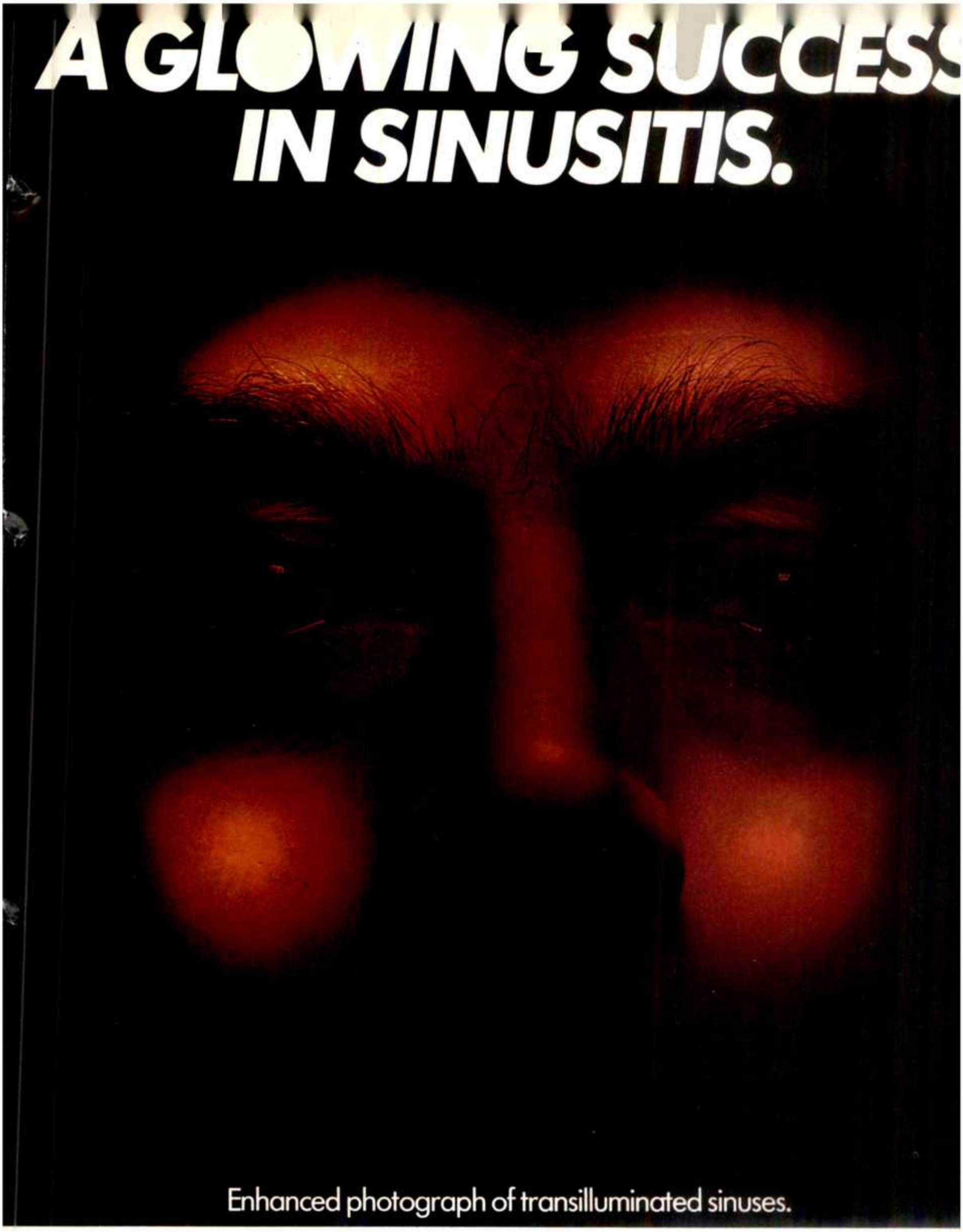

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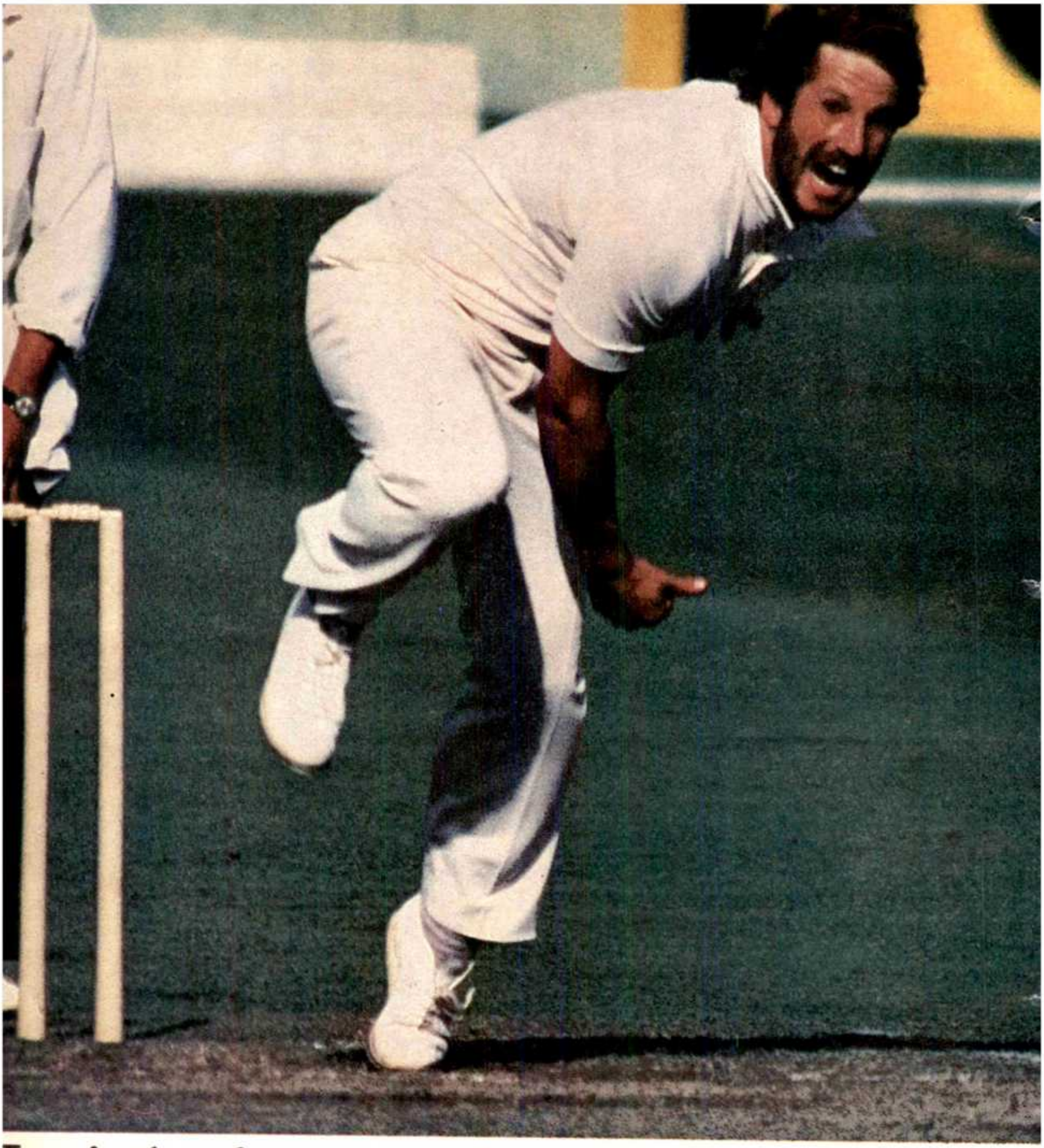

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Controversy

A NEW LOOK AT ADULT ASTHMA

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> 'If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties.
>
> FRANCIS BACON (1561–1626)
> *Advancement of Learning*, I, 8

Summary

Understanding of the natural history of asthma is hampered by the lack of precise definitions. A new definition of severe acute asthma is proposed with primary emphasis on the circulatory disturbances. The natural history of severe acute asthma and the value of steroid therapy are re-examined in the light of the new definition.

INTRODUCTION

Although little is known about the fundamental causes of asthma, clinical patterns of presentation are similar, irrespective of cause. Physicians have therefore adopted functional descriptions to assist them with therapy and research. These include continuous symptomatic asthma (chronic asthma), gradually deteriorating airway obstruction (synonymous with worsening of continuous symptomatic asthma), severe acute asthma (formerly status asthmaticus) and labile asthma. These definitions are not mutually exclusive and patients frequently change from one pattern to another. The change is never instantaneous or discrete and it is during the transition that difficulty with terminology has arisen. When a patient with continuous symptomatic asthma develops increasing symptoms, at what stage does one call it severe acute asthma? The definition of severe acute asthma adopted by Clark (1977) is an episode of asthma of increased severity failing to respond to more than average treatment. Such a definition could equally apply to gradually deteriorating airway obstruction. This imprecise nomenclature has led to confusion, the natural history of severe acute asthma being variously described as ranging from hours to weeks (Macdonald et al. 1976; Howard 1978; Davis et al. 1980). Similarly, the lack of precision of the term severe acute asthma may discredit some of the earlier research into it. This may be particularly important in considering the efficacy of steroid therapy in severe acute asthma.

TERMINOLOGY

The author believes that gradually deteriorating airway obstruction and severe acute asthma are distinct entities with separate pathophysiologies. Thus, the hallmark of severe acute asthma is the circulatory disturbance ranging from tachycardia, through pulsus paradoxus to hypotension and circulatory collapse. These circulatory effects are part of the primary disturbance and not secondary to hypoxaemia.

It is only by assuming separate pathologies that it is possible to explain the frequent observation that, of two groups of asthmatic patients with similar degrees of airway obstruction, the patients with gradually deteriorating airway obstruction, although disabled by effort dyspnoea, have normal heart rates and are able to continue with their daily routine, while patients with severe acute asthma have circulatory effects which threaten their very existence. A second reason for believing that the circulatory effects are of primary importance in severe acute asthma can be derived from work of Rees et al. (1967) who studied the clinical course and arterial blood-gas tensions of 25 patients with severe acute asthma. In patients who recovered there was a clinical improvement, as manifest by decreasing heart rate and return of normal blood pressure, many days before an appreciable change in the degree of hypoxaemia. This contradicts the commonly held view that circulatory effects are secondary to hypoxaemia. Moreover, in three patients who died the most striking feature was the persistence and worsening of circulatory disturbance. Another reason for suspecting that gradually deteriorating airway obstruction and severe acute asthma are separate conditions and not merely a continuum of the same process is that severe asthma provokes a stress response (Collins et al. 1975*b*) plasma cortisol levels rising in proportion to severity, while continuous symptomatic asthma does not (Soutar et al. 1975).

STEROID THERAPY

While steroid therapy has proved to be very effective in relieving the airway obstruction associated with continuous symptomatic asthma (Ellul-Micallef et al. 1974; Ellul-Micallef & Fenech 1975), there has been comparatively little research to investigate the value of steroids in severe acute asthma. Since most physicians have tended to assume that severe acute asthma is merely a progression from gradually deteriorating airway obstruction, logic has demanded the use of steroids. However, if the two conditions are distinct as suggested, then we must once again re-examine our therapies. The definitive study into the efficacy of steroids in severe acute asthma was carried out under the auspices of the Medical Research Council in 1956. In the light of modern knowledge, this study can be criticized on four counts. First, the number of patients studied was too small. Secondly, the concomitant use of sedatives, which was an integral part of the trial, is now known to be hazardous. Thirdly, the failure to define 'status asthmaticus'. The apparent efficacy of steroids in this trial may have been due to the fact that a proportion of the patients treated successfully had been suffering from a deterioration of continuous symptomatic asthma rather than severe acute asthma. Finally, the doses of steroids used in the trial were physiological rather than pharmacological, suggesting that the cortisol levels achieved would have been unlikely to exceed those found normally in the stress response to acute severe asthma. 'Unless previously treated with systemic corticosteroids, asthmatic patients respond normally to stress' (Collins et al. 1975*a*). Hence in severe acute asthma, plasma cortisol levels are significantly correlated with the degree of acidaemia and heart rate. If steroids are beneficial in severe acute asthma, why then does not endogenous cortisol act therapeutically in this situation? I have successfully treated more than 60 patients with severe acute asthma without recourse to massive steroid therapy, and the results suggest that steroids are ineffective in the treatment of acute severe asthma (Luksza 1982).

NATURAL HISTORY OF SEVERE ACUTE ASTHMA

Since the definition of severe acute asthma is imprecise, the natural history of the attack has been variously estimated as ranging from hours to days. This discrepancy can be resolved if terminologies are re-examined. I believe that severe acute asthma, as distinguished by circulatory effects, develops rapidly over hours either from a state of normal respiratory function as in labile asthma or, more commonly, from a background of gradually deteriorating airway obstruction. Thus, Bellamy and Collins (1979) described poorly controlled wheezing for a mean period of five weeks before a more rapid deterioration, usually over 24 hours, caused patients to seek medical attention. Similarly, Davis et al. (1980) observed deteriorating asthma for a mean period of 14 days before a more rapid descent associated with the onset of tachycardia.

Since the majority of attacks of severe acute asthma are superimposed on a prolonged period of poor control, it is likely that gradually deteriorating airway obstruction predisposes to severe acute asthma. Thus steroids, by treating gradually deteriorating airway obstruction, may prevent the advent of the severe attack.

ASTHMA DEATHS

Although advances in treatment have transformed the lives of many chronic asthmatics, the mortality rates for asthma have not altered substantially for over 100 years (Speizer & Doll 1968). Most asthma deaths occur outside hospital as the result of attacks of severe acute asthma (Bellamy & Collins 1979). A significant number of hospital deaths from asthma occur unexpectedly from ventilatory arrest in the presence of an excessive diurnal variation in peak expiratory flow rate (Hetzel et al. 1977).

Underuse of corticosteroids is frequently cited as a cause of continuing mortality from asthma (Ormerod & Stableforth 1980; Macdonald et al. 1976) yet the death rate has not decreased since their introduction in the late 1950s. Steroid therapy should avert death by preventing attacks of acute severe asthma. If we assume that as few as one-third of asthmatic patients are being appropriately treated with corticosteroids, then surely we should expect a decreasing incidence of severe acute asthma and a falling mortality rate. I suspect that while there is a decreasing incidence of acute severe asthma, the case fatality rate is increased. The reasons for this are unclear but may be related to inappropriate use of steroids.

There was an epidemic of asthma deaths in the mid-1960s ascribed by many to the overuse of isoprenaline aerosols (Inman & Adelstein 1969). During severe acute asthma, a combination of mucus plugging, inadequate tidal volume and inability to breath-hold serve to make pressurized aerosols an ineffective delivery system (Gregg 1980). It is therefore unlikely that lethal doses of isoprenaline were administered by this route. Hydrocortisone has been shown to potentiate the cardiotoxicity of isoprenaline (Lehr 1972) and it is possible that sublethal doses of isoprenaline, in the presence of hypoxaemia and systemic steroid therapy, may have been sufficient to produce toxicity resulting in death. Far from preventing asthma deaths, steroids may well have contributed to them.

Finally, it has been shown that steroids do not influence the liability to morning dipping and would therefore be unlikely to reduce hospital mortality related to this cause (Soutar et al. 1975).

CONCLUSIONS

1. Severe acute asthma and gradually deteriorating airway obstruction are distinct clinical conditions.
2. Severe acute asthma is distinguished from gradually deteriorating airway obstruction by its profound circulatory effects, ranging from tachycardia to cardiac arrest.
3. Severe acute asthma develops rapidly either from a background of normal respiratory function in labile asthma or, more commonly, from a prolonged period of gradually deteriorating airway obstruction.
4. Steroids may prevent the onset of severe acute asthma by treating gradually deteriorating airway obstruction but they are ineffective once severe acute asthma is established.
5. Systemic steroid therapy may have contributed to the epidemic of asthma deaths in the mid-1960s by enhancing the cardiotoxicity of isoprenaline.

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ACUTE SEVERE ASTHMA TREATED WITHOUT STEROIDS

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Summary

Sixty patients with acute severe asthma were treated by conventional methods in all respects except for the use of steroids. Patients who were not currently taking systemic steroids (30) received none during the severe attack, and those who were currently taking systemic steroids (30) were given 400 mg hydrocortisone daily. The results were compared to a further group of 30 patients with acute severe asthma of similar severity who were treated in the same hospital by the same methods but with much larger doses of hydrocortisone (1200 mg daily). All 60 patients recovered and the time course, changes in heart rate and peak expiratory flow (PEFR) were similar in all groups. These results suggest that steroids are of doubtful value in the treatment of acute severe asthma and further randomized and controlled trials are required.

INTRODUCTION

In contrast to chronic asthma where the benefits of corticosteroids are well documented (Ellul-Micallef 1972; Ellul-Micallef et al. 1974; Ellul-Micallef & Fenech 1975); their value in acute severe asthma is based on only one controlled trial conducted as long ago as 1956 (MRC 1956). Since then the recommended dose of hydrocortisone for treating the acute attack has increased fourfold (Collins et al. 1970, 1975) and the definition of acute severe asthma has been revised (Clark 1977); Cayton & Howard 1973). The original trial is therefore no longer valid.

The mortality from asthma has not changed since the introduction of steroid therapy. Despite large doses of hydrocortisone, some patients with acute severe asthma continue to deteriorate and require treatment by intermittent positive pressure ventilation (IPPV). For these reasons the present study of steroid therapy in acute severe asthma was designed.

Patients and Methods

Ninety patients with acute severe asthma admitted to the Intensive Care Unit over a period of three years were studied. Those eligible for entry were over 16 years of age, with an established history of reversible airways obstruction. For the purposes of the study acute severe asthma was defined as a rapid deterioration in airway obstruction severe enough to cause immobility and associated with a tachycardia of at least 100 beats/minute.

All 90 patients received identical and conventional therapy in all respects except for steroid therapy. Thus, the first 30 patients admitted during the trial period received conventional high doses of hydrocortisone, being given 100 mg hydrocortisone two-hourly by intravenous injection.

This group comprised 18 patients who were not currently taking oral steroids for maintenance and 12 who were receiving regular steroids. Subsequently, patients who were not taking oral steroids for maintenance therapy received none during their acute attack (30 patients), while patients taking regular oral steroids received only 400 mg of hydrocortisone daily. This dose was adopted from the findings of a study by Plumpton et al. (1969) who showed that 400 mg hydrocortisone daily produced plasma cortisol values comparable to those seen during stress. Conventional therapy given to all patients comprised continuous 35% oxygen delivered by Ventimask, an intravenous 3 litre clear fluid regimen for rehydration, a continuous infusion of aminophylline at a rate of 0.9 mg/kg/hour (Jones 1980) and nebulized salbutamol, four-hourly, delivered by intermittent positive pressure breathing (Mark VII Bird Ventilator).

An initial assessment of severity was made in all 90 patients by recording the heart rate on admission, the peak expiratory flow rate (PEFR) on admission (expressed as a percentage of the predicted value for age and sex) and a subjective index of severity using the grading system devised by Gett (Jones 1971) (Table I). PEFR was measured with a Wright peak flow meter and the best of three attempts was recorded. Thereafter, progress was assessed by recording the duration of hospital stay and the changes in PEFR and heart rate monitored 12-hourly for the first 48 hours.

Table I. Method for grading severity of asthma

1	Patient able to carry out housework or job with some difficulty
2	Patient able to carry out housework or job with great difficulty
3	Patient confined to bed or chair but able to get up with moderate difficulty
4	Patient confined to bed or chair but able to get up with great difficulty
5	Patient totally confined to bed or chair
6	Patient moribund

After Jones (1971).

RESULTS

For purposes of analysis, the patients were divided into four groups (Table II). Thus, groups 1 and 2 comprised patients not normally on oral steroids for maintenance therapy. Group 1 consisted of 30 patients treated without hydrocortisone during the acute attack and group 2 comprised 18 patients treated by the same methods together with hydrocortisone 1200 mg daily. Groups 3 and 4 comprised patients who were normally receiving oral steroids. Group 3 comprised 30 patients given only 400 mg hydrocortisone daily during the course of acute severe asthma and group 4 comprised 12 patients who received 1200 mg hydrocortisone daily. The four groups were well matched for age, initial heart rate, PEFR and clincial grade of severity (Table III).

Among the 90 patients treated, there was one death. This occurred in a 56-year-old woman from group 2, a non-steroid dependent asthmatic treated with high doses of hydrocortisone. Death resulted from a *Pseudomonas* pneumonia during assisted ventilation.

Intubation and mechanical ventilation (IPPV) was required on 13 occasions. This included six patients from group 1, four from group 2, one from group 3 and two from group 4. The indications for IPPV were exhaustion in 11 patients and inappropriate sedation in two. In four of six patients from group 1 who required IPPV, this treatment was started within two hours of admission, and it is therefore unlikely that treatment with hydrocortisone could have averted the necessity for mechanical ventilation in these patients.

Table II. Allocation of patients into four treatment groups

Maintenance therapy	*Group*	*No. of patients*	*Steroid treatment*
No steroids	1	30	No steroids
	2	18	Hydrocortisone
Regular steroids	3	30	Hydrocortisone 400 mg daily IV
	4	12	Hydrocortisone 1200 mg daily IV

Table III. Comparison of severity of acute severe asthma on admission (means ± SEM)

	No steroids		*Regular steroids*	
Treatment group	1	2	3	4
Age (years)	28.7±2.2	32.1±3.8	45.1±5.4	44.3±3.7
Heart rate (beats/minute)	131±2.9	132±3.3	131±3.0	133±4.1
PEFR (% predicted)	20.9±2.1	19.3±3.3	19.9±1.0	21.0±2.2
Clinical grading	4.9±0.2	4.9±0.2	4.7±0.1	5.2±0.2
IPPV	6	4	1	2

Using covariance analysis and performing Student's *t*-tests on the adjusted means, group 1 was compared to group 2, and group 3 compared to group 4 for the following variables: the percentage change in heart rate measured at 12-hourly intervals for the first 48 hours; the percentage change in PEFR at daily intervals for the first two days; and the duration of hospital stay. In no instance was there any statistically significant difference between the groups (Table IV, V, VI). There was an impression that progress was more favourable for patients treated without hydrocortisone. Thus, patients not taking regular steroids who were treated without hydrocortisone stayed in hospital for a mean period of 3.9 days compared to 5.3 days for similar patients given hydrocortisone. Similarly, the percentage improvement in PEFR was 179% in patients from group 1 treated without hydrocortisone compared to 121% for patients given the same treatment together with high doses of hydrocortisone.

Table IV. Percentage decrease in heart rate (mean) during acute severe asthma

Time from admission (hours)	*Patient group* 1	2	*P*	*Patient group* 3	4	*P*
12	14.4	16.3	0.68	14.7	11.0	0.29
24	23.4	19.0	0.43	19.1	13.6	0.19
36	29.5	25.5	0.51	26.3	21.1	0.24
48	31.3	24.7	0.30	31.0	23.9	0.09

Table V. Percentage increase in PEFR during acute severe asthma

Time from admission (hours)	*Patient group* 1	2	*P*	*Patient group* 3	4	*P*
24	126.8	67.8	0.13	74.9	65.0	0.61
48	179.1	121.4	0.12	111.2	89.3	0.40

Table VI. Duration of hospital stay

	Patient group 1	2	*P*	*Patient group* 3	4	*P*
Duration of stay (days)	3.9	5.3	0.16	5.0	5.6	0.49

DISCUSSION

Acute severe asthma, formerly known as status asthmaticus, is difficult to define and this makes it difficult to prove the value of one or more treatments. The definition in this study was based on the disability caused by dyspnoea and fatigue together with a tachycardia. The author contends that the latter is crucial to the definition of acute severe asthma, distinguishing it from deteriorating chronic asthma. This theme is expanded elsewhere (Luksza 1982).

In the present trial, the variables studied were not influenced by treatment with intravenous hydrocortisone. It is possible that other parameters might have shown differences, although this is unlikely to be so for hypoxaemia which correlates with the heart rate (Rees et al. 1967). Nevertheless, it should be stressed that this pilot study, although controlled, was not randomized and further properly designed randomized trials will be required to see if the results are reproducible. Moreover, the definition of acute severe asthma in future trials must be identical to allow a true comparison.

Another potential criticism of the present study was the high proportion of patients requiring mechanical ventilation. It should be remembered, however, that the group studied fulfilled the criteria for admission to the intensive care unit (Jones 1980) and thus represented only a small percentage of total asthma admissions to the hospital.

The pathophysiology of both acute and chronic asthma includes bronchospasm and the formation of mucus plugs, but as yet there is no method of quantifying the amount of obstruction to airflow due to each process. If steroids are effective in chronic asthma, but ineffective in acute severe asthma, then the results suggest that the mechanisms of airway obstruction may be different in the two conditions.

The results of the present trial, if substantiated by further studies, may be of more than academic interest. It is pertinent to note that both the death in the present study and the only death in the original MRC Trial (1956) occurred in steroid-treated patients and in both instances death resulted from overwhelming sepsis. Steroid therapy, by causing immunosuppression, may have been an important contributory factor.

ACKNOWLEDGEMENTS

The author is grateful for the receipt of a personal grant from the Mersey Regional Health Authority. The scheme of research is part of a project (research scheme No. 366) made possible by a grant to Dr E. Sherwood Jones. The author is similarly grateful to Allen and Hanbury's Ltd. for financial support.

Requests for reprints to Dr A. R. Luksza, Whiston Hospital, Prescot, Merseyside.

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Comments by Dr I. W. B. Grant on these two papers by Dr Andrew R. Luksza will appear in the April 1982 issue (76/2).

Br. J. Dis. Chest (1982) *76*, 20

Does the Lung Work?

3. SHEDDING LIGHT ON THE SUBJECT

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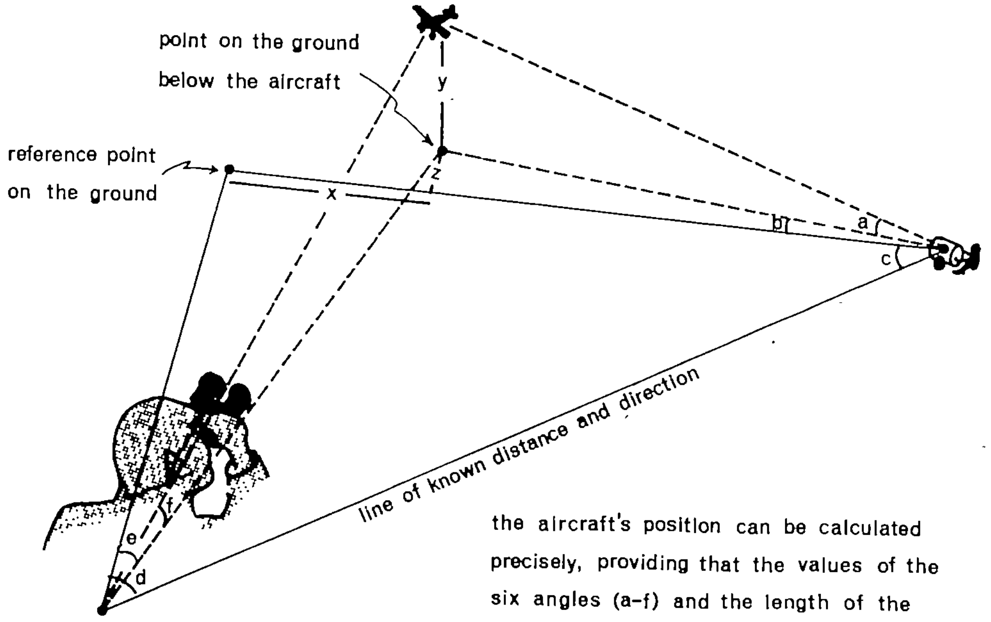
Lung Function Unit, Brompton Hospital, London, and IBM (UK) Scientific Centre, Winchester

Luckily for surveyors and geographers, and for anti-aircraft gunners, light travels in straight lines and so, at night, if one man traps an aircraft in a searchlight's beam, another person standing a known direction and distance away can calculate its position with precision by simple trigonometry (Fig. 1). It is possible to determine the position of every point on the thoracoabdominal wall, using the same principle (Fig. 2). Since a pair of cameras can record all of the information from both aspects of the body instantaneously and repeatedly, the size, shape, position and motion of the whole of its surface can also be determined in detail with great accuracy.

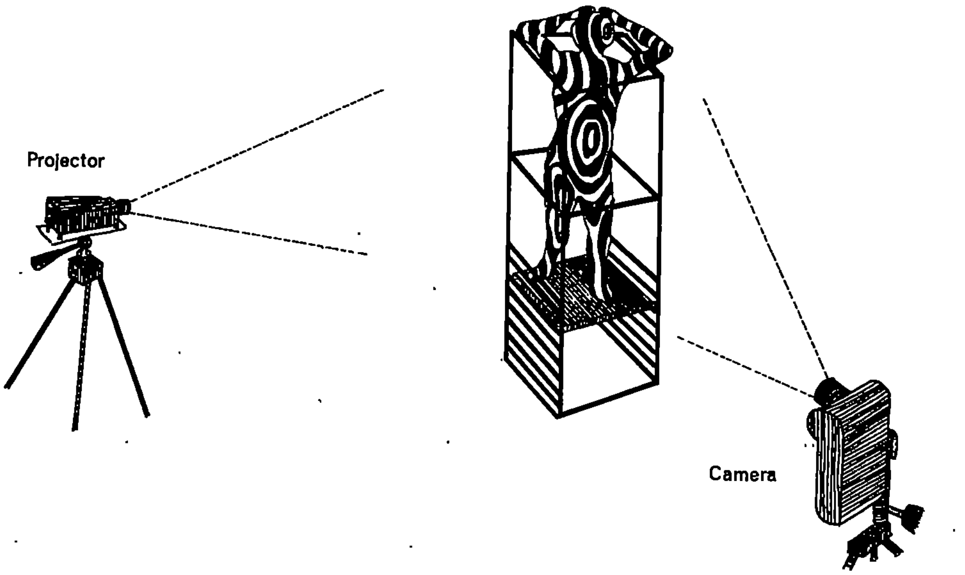
Many people have explored this approach in the past (e.g Kovats 1970, 1974; Herron 1972; Lovesey 1973; Williams 1977), but until recently it has not been of practical interest because of the tedium of measuring all the distances on the photographs and calculating their origins in real space, since something like a thousand points are needed



the aircraft's position can be calculated precisely, providing that the values of the six angles (a–f) and the length of the reference line are known.

Fig. 1. Using a light beam and a light sensor to determine the x, y and z coordinates of a point in space, relative to any arbitrary point of reference and set of axes

View of the recorded image



General view – photographic system

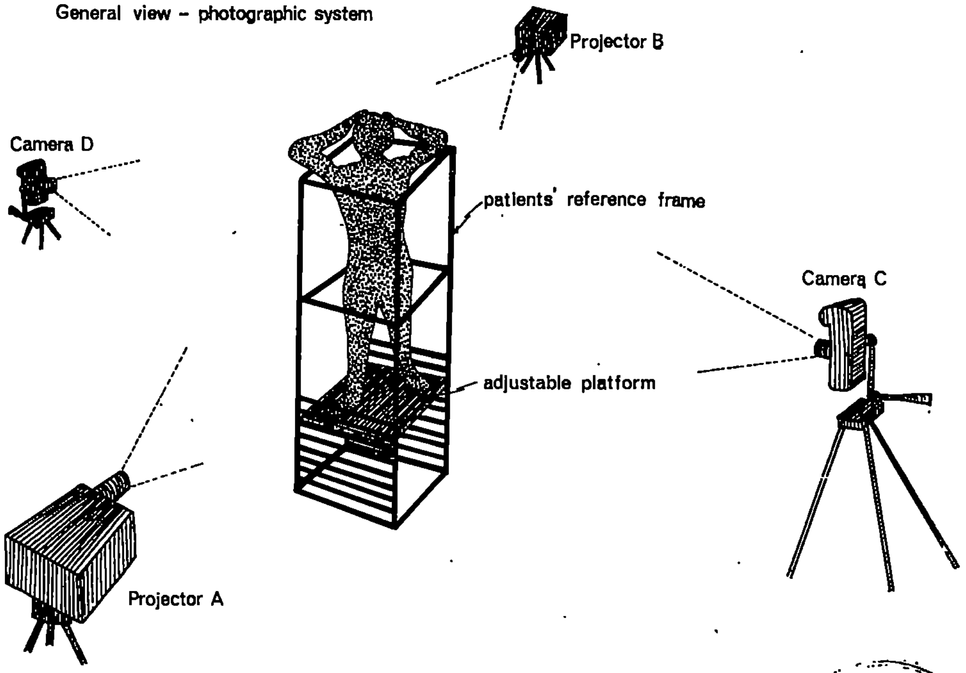


Fig. 2. Applying the same principle as in Fig. 1 to determine the position of any set of points on the surface of the torso

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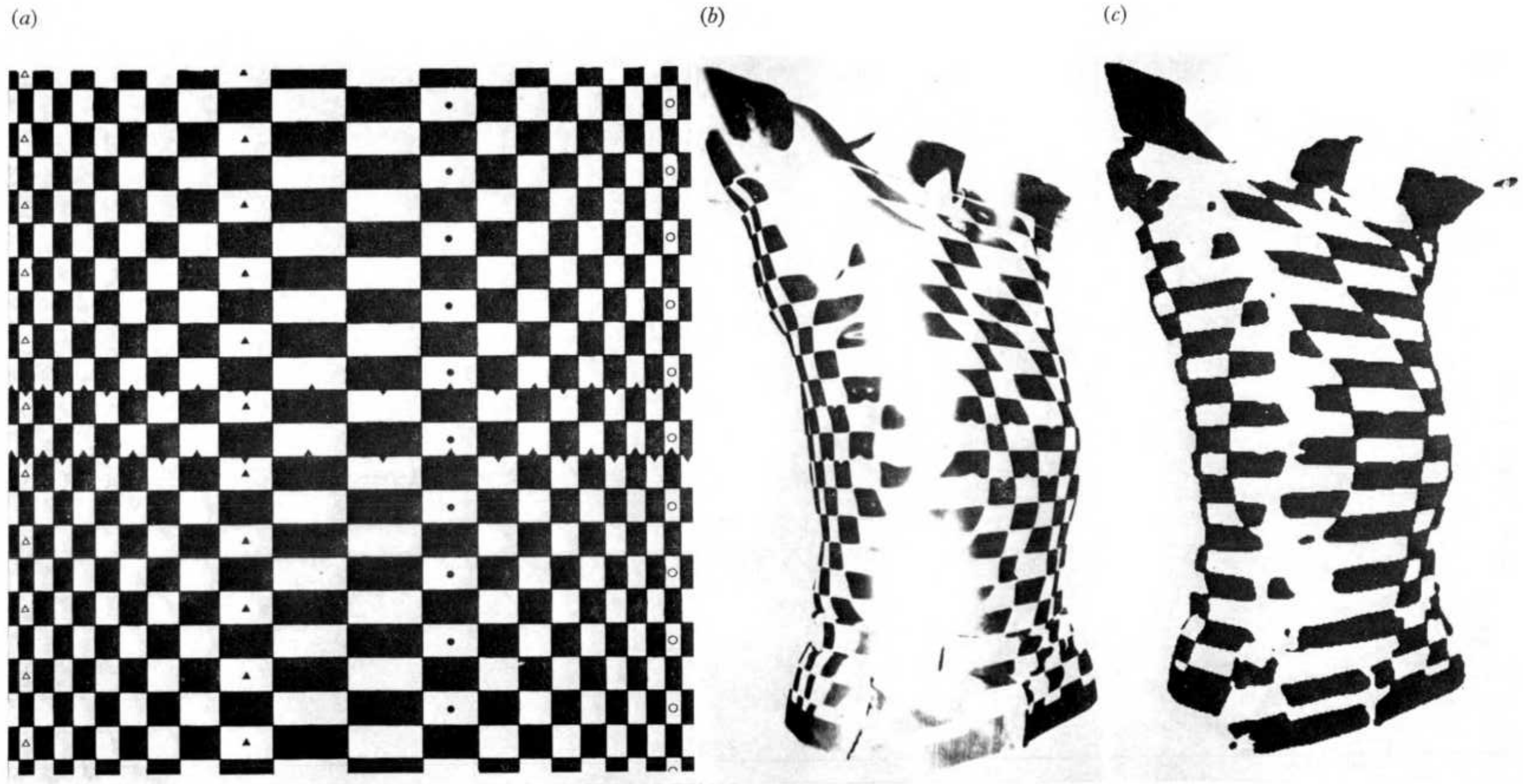


Fig. 3. (*a*) A logarithmic chess-board pattern that casts roughly equidistant points on the surface of a cylinder. (*b*) Photographic image of the trunk of a normal young man, illuminated in this way. (*c*) A digital reconstruction of (*b*) after it had been read automatically by a scanning densitometer, and the contrast between light and dark had been enhanced.

to describe the trunk accurately enough for physiological purposes. Modern image-processing techniques have changed all this and it is now possible to read photographs automatically with a scanning densitometer, as in Fig. 3, or to record images of the chest in digital form directly, using video-cameras. If necessary, the images can be enhanced to sharpen their borders, corrected for any known optical distortion and then analysed automatically. The four-dimensional information that results (three spatial dimensions and time) can then be presented in any digital or graphical form. Because this is so, it is reasonable to ask what can be learnt about breathing from knowing the shape and motion of the trunk in such detail.

First, single pairs of photographs record the shape of the chest at a particular moment, in a convenient form for patients' notes, that do not necessarily need detailed analysis at the time. Obviously they are especially helpful in conditions such as scoliosis (Fig. 4). Series of photographs over longer periods of time will show how the chest changes shape from infancy to senescence (cf. Burke 1979) and are already used in screening programmes on schoolchildren, to detect scoliosis at an early stage (Adair et al. 1977; Inoue et al. 1977).

Secondly, pairs of photographs at the beginning and end of an inspiration can be used to determine the size and spatial distribution of the breath, to demonstrate any

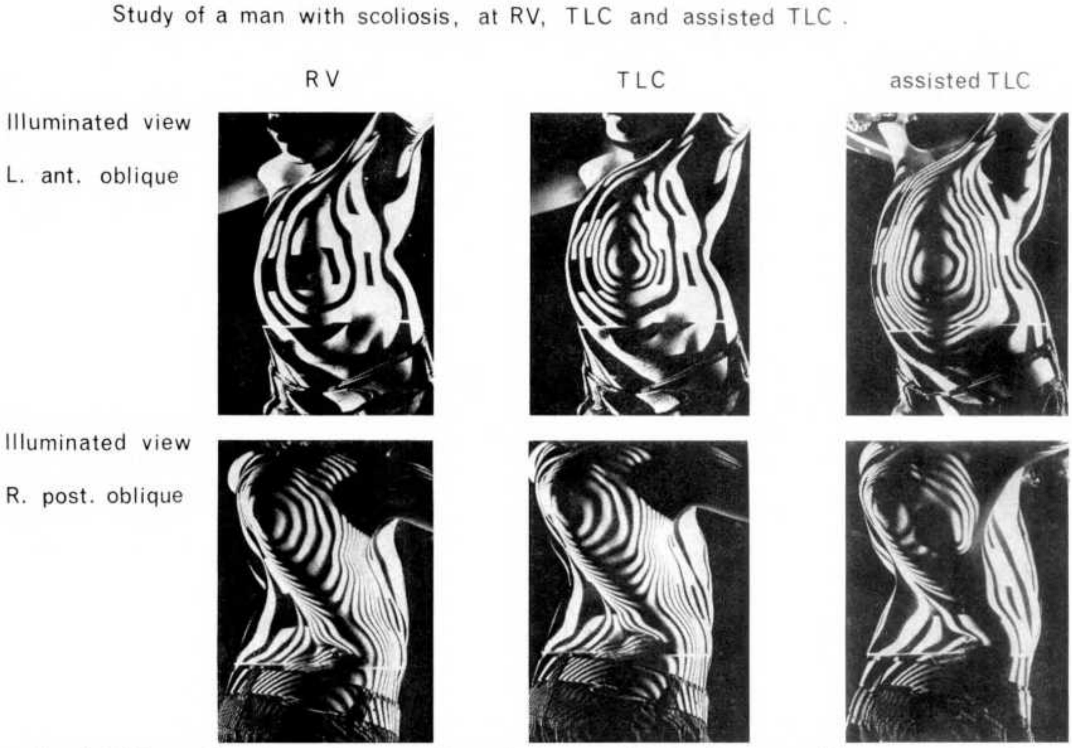
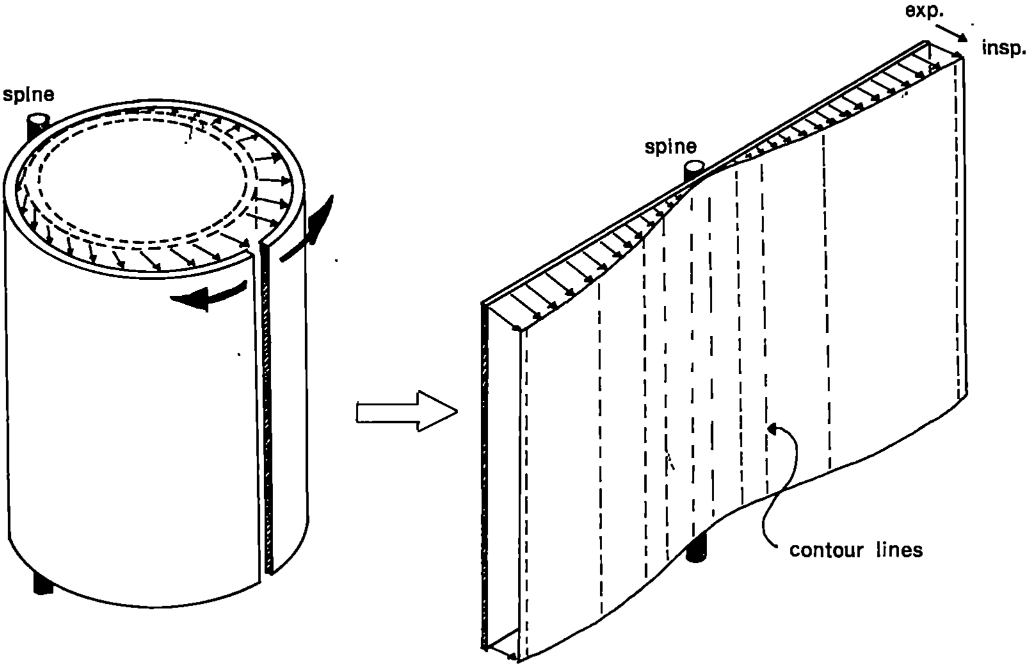


Fig. 4. Light-section views of a man with scoliosis, at residual volume, total lung capacity and at total capacity with the assistance of a Cape ventilator. Note that the increases in chest volume, as judged by the number of contour lines, take place almost entirely anteriorly. The increase in capacity with the ventilator is also obvious

It is easy to unwrap the surface of an expanding cylinder and demonstrate the relative contributions of various parts to the overall increase in volume :



In this case, the contour map shows horizontal and vertical asymmetry of motion :

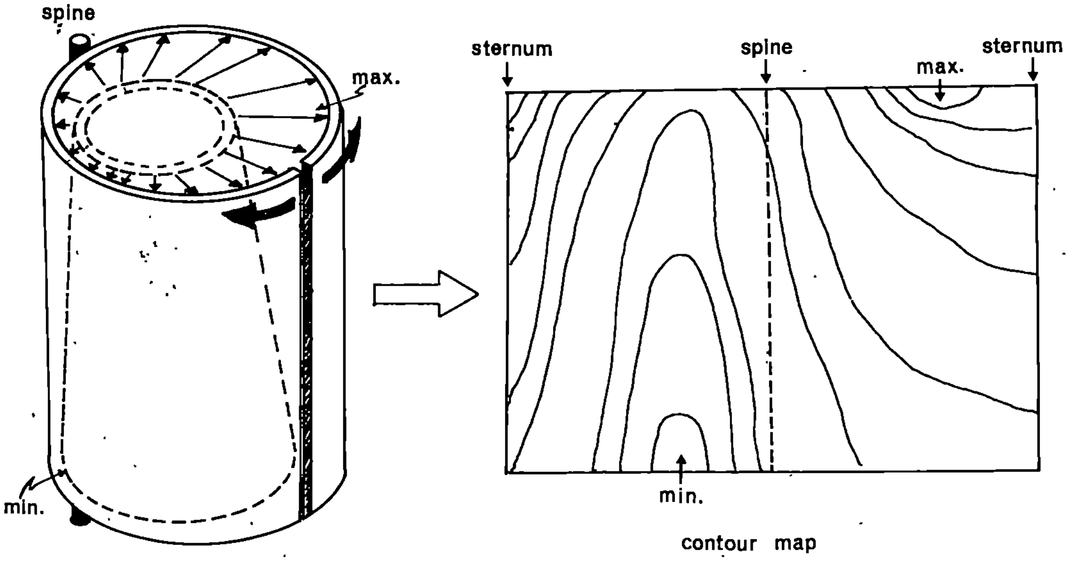


Fig. 5. A method of presenting the distribution of motion over the unwrapped surface of an expansile cylinder

It is possible to divide views of the surface that moves, into units of equal area, and to shade or colour each unit according to its contribution to overall volume change.

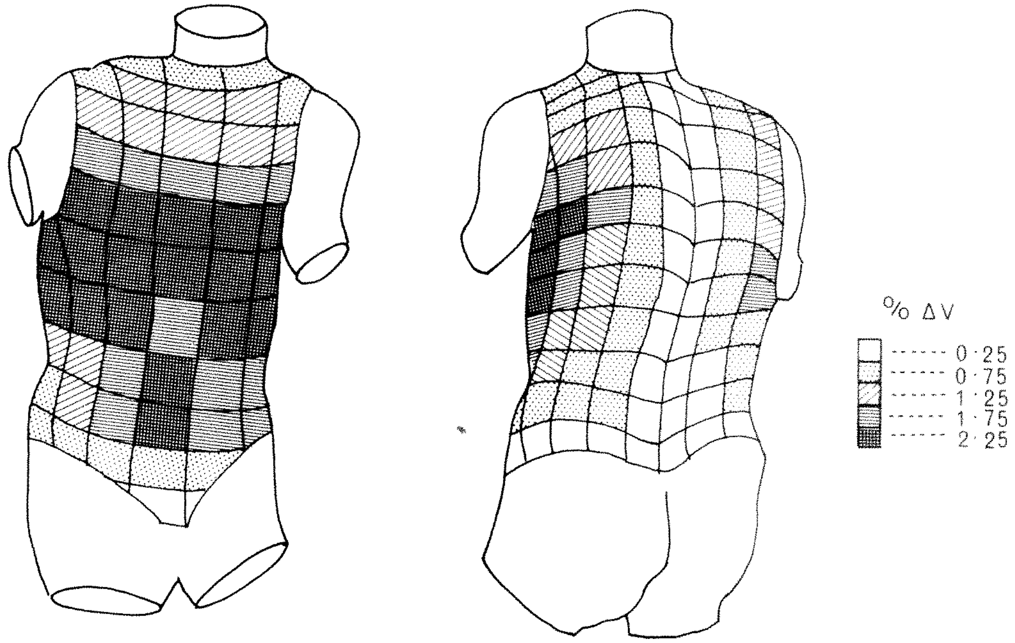


Fig. 6. A method of indicating the distribution of respiratory motion on the surface of the thoraco-abdominal wall

asymmetries and to identify and measure the relative contributions of rib-cage and diaphragmatic motion. They can also define areas of paradoxical movement. However, providing this data in a rapidly intelligible form creates a problem of data presentation, since it is not easy to show four-dimensional information on a two-dimensional sheet. If the chest were a cylinder that only expanded radially its surface could be unwrapped as in Fig. 5, to provide a contour map of surface motion. Unfortunately, more complex shapes and motions cannot easily be unwrapped and described in the same way, but it is possible to superimpose the information on orthodox body images, dividing each surface up into elements of equal area and shading or colouring each element to indicate its contribution to the breath in question (Fig. 6).

This approach is intuitively attractive, but not as simple as it looks, because it begs two vital questions:

1. Which contributes most to shifting a load, the moving lever or the stationary fulcrum?
2. When a body translates or rotates (rigid body motion), and changes form at the same time, how can we distinguish the origins of the change in form?

One course is to identify a rigid element (e.g. the sternum) on the surface, suppose it has not moved, poise both shapes about it and then compare dimensions, recognizing that diametrically opposite results would be obtained if the spine had been accepted as an 'immobile fulcrum'. Another course is to use the rigid element as a guide to orientation rather than position, calculate the 'centre of gravity' (strictly the centroid of volume) of each shape, align the shapes so that their centroids and axes of orientation coincide and then compare their dimensions. These difficulties are particularly obvious when thinking of the shape changes which occur during breathing, in people lying on their front, side or back. There does not seem to be a simple theoretical solution to this problem; it has to be tackled by adopting a convention and comparing the results seen in an individual patient with those seen in an appropriate group of normal people.

These considerations do not interfere with a third application, optical plethysmography, in which it is only necessary to know the volume of the trunk and not the changes in specific dimensions. Since rays of light can be used to determine the volume of the trunk, by summing the volumes of a series of imaginary horizontal slices, they can also be used to determine the flow–volume loop, the thoracic gas volume and the effective pulmonary blood flow. The first of these requires a series of 10 or more pairs of images through the breath so that flow can be determined from the successive changes in volume. The second needs images taken before and after blowing into a manometer. The manometer can be set to capture the second image when a particular pressure, e.g 50 mmHg, is reached. Blood flow is measured by inhaling a soluble gas such as nitrous oxide and recording the shrinkage in trunk volume while the breath is held and the gas absorbed, as in conventional whole-body plethysmography (Lee & Dubois 1955). For this purpose two pairs of images need to be taken at a known time interval, e.g. 20 seconds, but this also is easily automated.

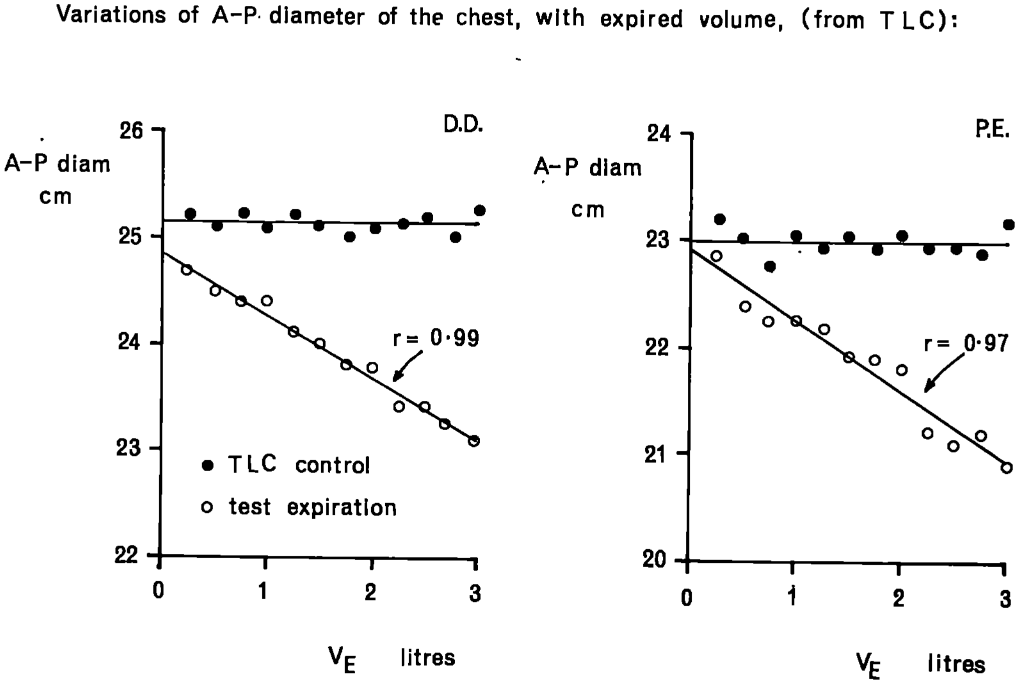


Fig. 7. Consecutive measurements of a particular anteroposterior chest diameter in two normal subjects, who first inspired to total lung capacity and then expired an increasing multiple of 250 ml on each of 12 occasions. Measurements were made with brass anthropometric calipers, while the subjects sat upright

Unlike the measurements of chest shape or vital capacity, these procedures require great accuracy because the volume changes produced by voluntary compression or soluble gas absorbtion are small and the alterations in wall position that have to be measured to detect these are smaller still. Chest diameters at total lung capacity are highly reproducible in healthy adults and diminish by a few millimetres for each litre of gas expired (Fig. 7). If the pressure in the chest is voluntarily raised by 50 mmHg, thoracic gas volume contracts by about 50/760, ie. 6.5% or roughly 300 ml. On average, chest diameters will then be some 2 mm shorter. Similarly, if a man inhales a vital capacity of 50% nitrous oxide and holds his breath for 20 seconds, his chest volume will fall by about 4% and the diameter will shrink by about 1.5 mm. These signals will need to be measured with 5–10% accuracy, that is to the nearest 20 ml volume and the nearest 0.1 to 0.2 mm in diameter! Can this accuracy be achieved?

At first sight it seems a tall order, but microscopists routinely use light to measure much smaller distances and geographers estimating the rate of continental drift or the distance of the Moon from the Earth, by optical means, achieve much greater resolution than the one part in a thousand called for here. The first requirement is an undistorted image that can be resolved into five hundred to a thousand elements, horizontally and vertically (i.e. up to a million 'pixels' in all). Next it is neccesary to decide how many point measurements are needed from this image to describe the trunk in sufficient

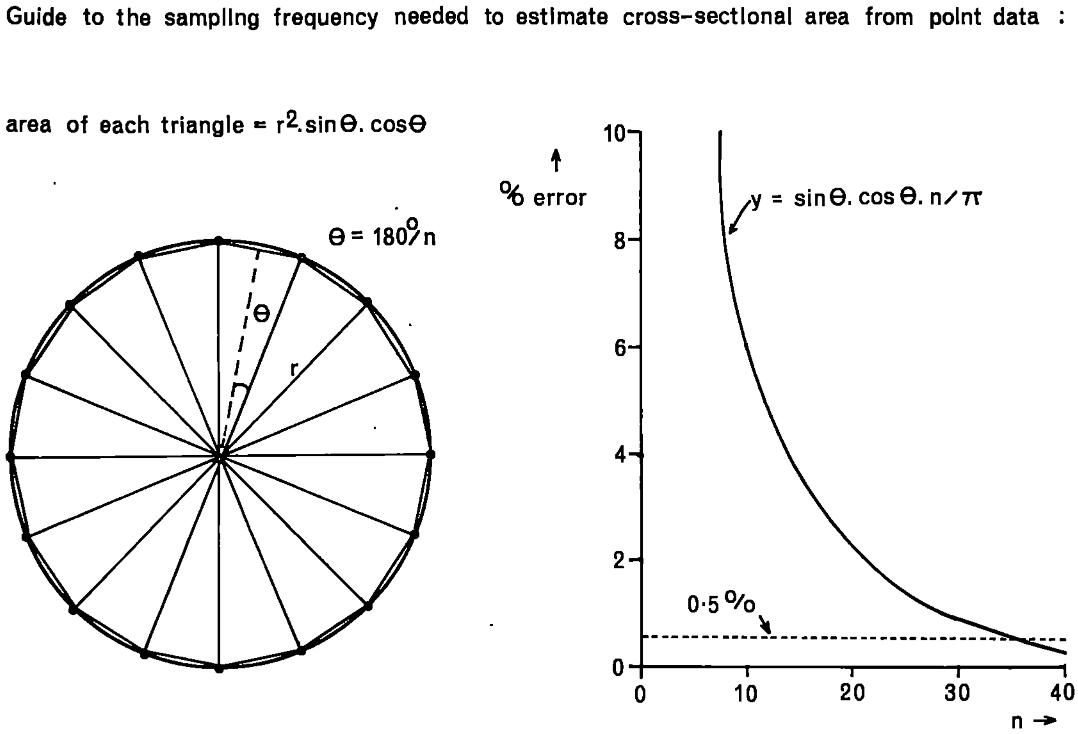


Fig. 8. The figure on the left compares the area of a circle and the polygon generated by 16 equidistant points on its circumference. The graph on the right shows how the percentage underestimate of the area falls as the number of points increases

detail. The answer to this problem is not simple, but can be approached by thinking of the chest in cross-section as a rough circle, the outline of which we know only from a number of equi-spaced points on its boundary. The simplest way of joining these points would be by straight lines, creating a polygon with an area somewhat less than that of the circle (Fig. 8). The error in the calculation of area falls below 0.5% when the number of points exceeds 35, suggesting that something like 40 points around a circumference will give the accuracy needed. Fitting the points by smooth curves will reduce the error further. Similar arguments apply to sampling in the vertical plane.

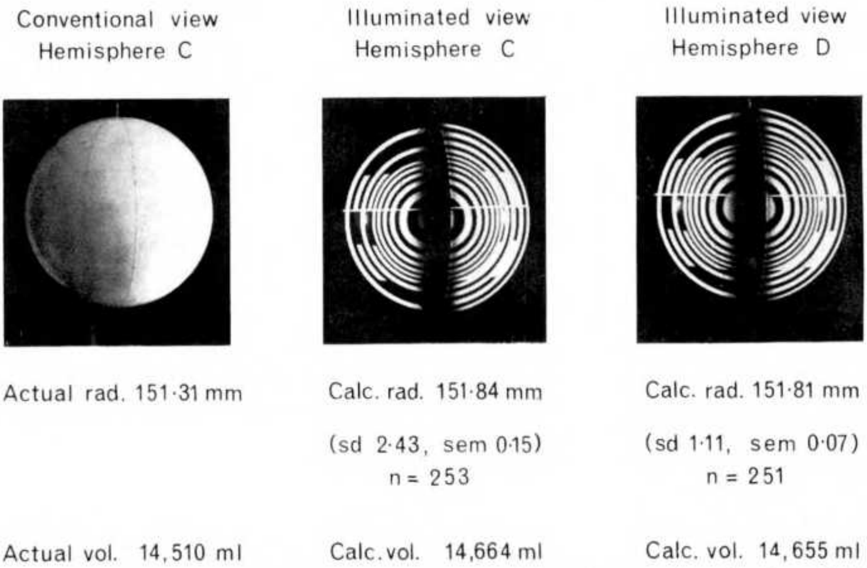


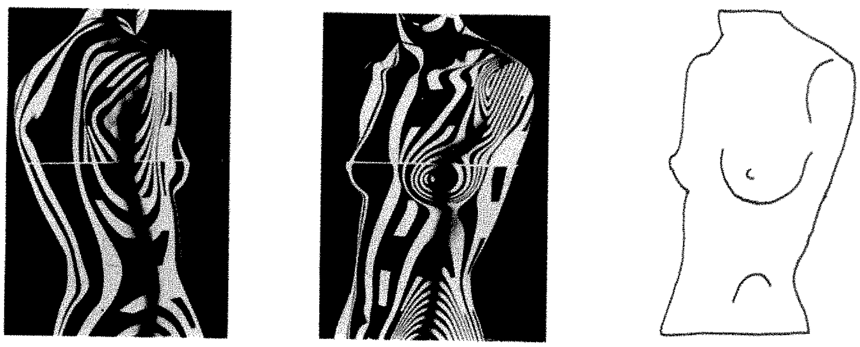
Fig. 9. Three views of a sphere known to have a radius of 151.31 mm and to displace 14 510 ml of water. The calculated radii and volumes of the two light-sectioned hemispheres were obtained from 35 mm 400ASA film taken at 1.6 m by two automatically synchronized Olympus OM2 cameras with standard lenses

If the chest supported a solitary porcupine spine, the position of which was unknown, and it was important to locate this feature and map out its size, the image would have to be sampled with much greater frequency. In general, extending the polygon argument further, sampling points need to be spaced at intervals of about $2\pi/40$, i.e. one-sixth of the smallest radius of curvature of the feature in question, to map it satisfactorily. The regeneration of a curved version of a three-dimensional surface from scattered points is quite a formidable problem, but various algorithms exist to do this.

Fig. 9 gives an idea of the accuracy that can be achieved in practice. It shows views of a sphere known to have a diameter of 151.31 mm. Its sphericity was checked by rotating it against a semicircular former of the same radius and observing that it did not deviate from that boundary by more than 1 mm at any stage. The position of some 250 points on each hemisphere were calculated from these photographs and the distance of each point from the estimated centre of the globe then determined and found to be 151.83 + 1.89 mm. The standard error of the mean is 0.06 mm, which implies an absolute volume uncertainty of 9 ml. Considering the fore and aft views as two attempts to estimate the volume of the same hemisphere gives an idea of reproducibility, in this case to 0.03 in 150 mm and to 8 in almost 15 000 ml. It is these last figures that have to be borne in mind when considering the needs of plethysmography.

A sphere is the most demanding structure to reconstruct in one sense (because of its high curvature) but the easiest in another, since illumination from both sides only leaves a small vertical ring in doubt (see Fig. 9), whereas the female trunk in particular is mercifully far from spherical but casts several shadows. However, positioning the body at 45° to the axes of projection is usually sufficient to eliminate these and allow the form to be recovered with acceptable accuracy (Fig. 10).

Studies on a dummy torso



R. post. oblique (Camera C) | L. ant. oblique (Camera D) | Actual vol. 16,985 ml
Calcul. vol. 17,197 ml

Fig. 10. Light-sectioned views of a tailor's dummy known to displace 17 197 ml of water. The calculated volume was obtained with the same optical system as Fig. 9

To estimate the volume of the trunk in this fashion, it is neccessary to have opposing images which can be 'stuck together' and this requires fixed camera and projection systems and an all-round view. This is difficult to realize with bed-bound patients, in whom early detection of unevenness or paradoxicality of motion may be especially important. In these cases, and more generally, moiré-photography is an easily applied alternative. It is one of the most important measuring techniques in precision engineering and has an extensive literature (see bibliography). It has been used to determine the shapes of objects as large as an aircraft and as small as the detail on a coin. In principle, a grid of light rays is projected onto a surface and the image it produces is compared with that which would have been obtained from a flat surface at a known angle and distance. The contour lines generated by the interference of the observed and predicted patterns describe the shape of the objects surface relative to the flat reference plane, and is easily accurate enough for most clinical purposes.

In simple systems, the contour lines have regular interruptions, produced by the predicted grid (as in Fig. 11). These are difficult to read automatically as the computer program cannot easily distinguish between an interruption and a genuine gap between contour lines. However, mechanical or microchip systems can wobble the grid in reality or in the computer memory, to blur out the interruptions without changing the shape or position of the contour lines. The lines can then be sharpened by other enhancement routines and read electronically. Compact, readily-portable, camera-projections systems are available and many papers describe their theory and clinical use. Much of this work has been done in Japan, but important contributions have also come from Harris and his colleagues at the Oxford Orthopaedic Engineering Centre in the UK and from Madden and Karlen in the USA.

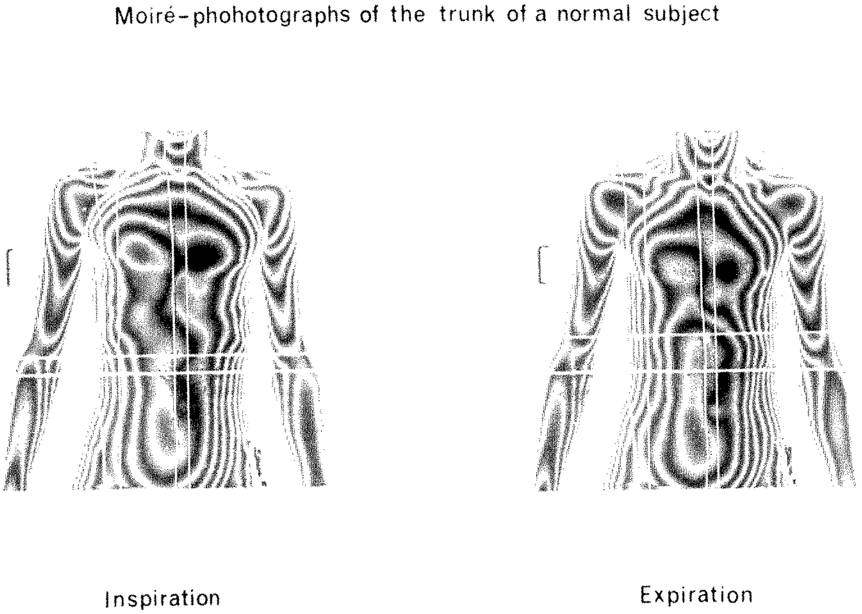


Fig. 11. Moiré photographs of the front torso of a normal man at total lung capacity and residual volume. (*Kindly provided by Dr J. D. Harris*)

The beauty of all these optical techniques is that they are physically non-invasive, they do not distort the variable they set out to measure and they do not introduce the thermal and humidity delays experienced in conventional plethysmography. They can also cope with people who are too ill or too anxious to enter a body-box. On the other hand, all photographs invade a person's privacy and must be taken and used considerately. Fortunately, the imposed light patterns show up well on ordinary underclothing providing it is tight-fitting, so the procedure is modest and easy to apply.

Breathing in consists of two processes, ascent of the ribs and descent of the diaphragm. Although the latter is invisible, the volume it excurses can be measured since the structures below it are incompressible, so the abdominal wall must excurse an equal amount. However, there is no way of telling immediately whether a poor abdominal excursion is due to generalized weakness of the diaphragm or paresis of one of its cupolae (but variations in vital capacity, when lying on one side and the other, are a guide). Nevertheless, the limitation could also be due to stiffness of the lung, diaphragm or abdominal wall, hyperinflation of the lung or weakness of the abdominal wall. Some idea of the quantitative contributions of the ribs and diaphragm can be obtained by comparing postero-anterior and lateral radiographs of the chest at residual volume and total lung capacity, especially if the two images are superimposed using the sliding grid technique mentioned by Hellstrom (1969). Here also, assessing the relative contributions of the diaphragm and ribs is complicated by the fulcrum and lever problem, since the diaphragm is believed to raise the ribs actively by contracting its arch against the fulcrum provided by a tense abdomen (Goldman & Mead 1973; Macklem 1981).

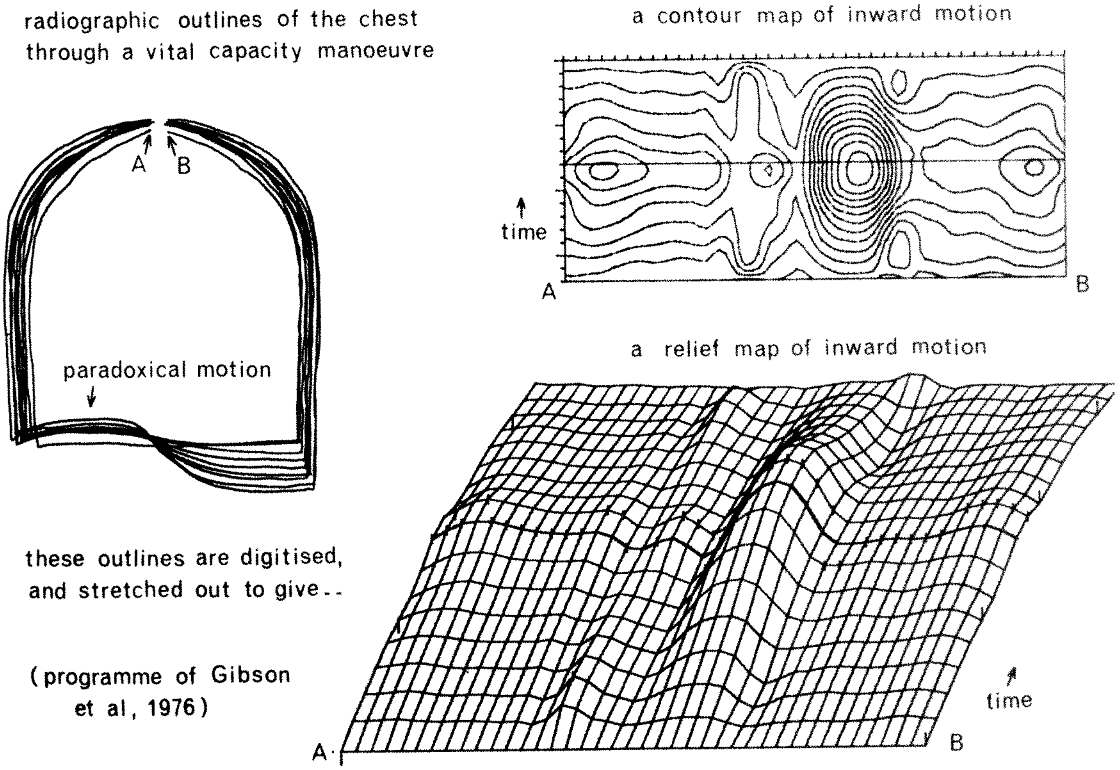

radiographic outlines of the chest through a vital capacity manoeuvre
A
B
paradoxical motion
these outlines are digitised, and stretched out to give..
(programme of Gibson et al, 1976)
a contour map of inward motion
time
A
B
a relief map of inward motion
time
A
B

Fig. 12. A method of displaying the motion of the ribs and diaphragm during a vital capacity manoeuvre—in this case from total lung capacity to residual volume and back again

Such measurements give no idea of the speed of motion of these structures. It is possible to obtain that information from video-taped images at fluoroscopy or from cine-radiography through a forced respiration (see, for example, Skarvan and Koci 1966; Hellstrom 1967, 1969). The data from a series of costophrenic outlines are not especially easy to analyse by eye, but can be displayed in a conveniently reduced form, using the techniques developed by Gibson et al. (1976) to study the motion of the left ventricular wall. In essence, the outlines are stretched out and then pulled towards or away from the observer, with time, producing the contour and relief maps of inward motion that are shown in Fig. 12.

The 'searchlight beam and observer' approach can also be used to give four-dimensional descriptions of the size, shape, position and motion of structures *within* the chest.

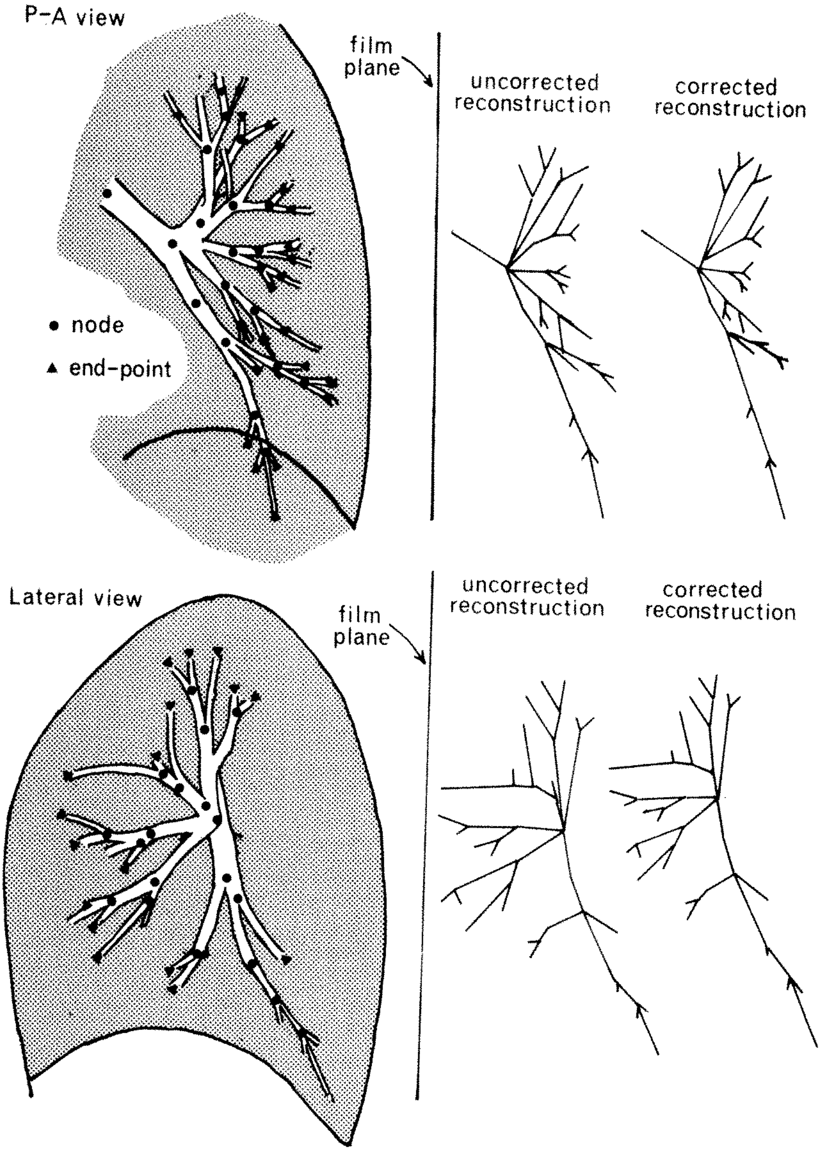


Fig. 13. Direct tracings and digitally reconstructed images of the bronchial tree, before and after correction for optical distortion. The computer program that provides these diagrams also lists the x, y and z coordinates of each node and the length of each element

Using identical trigonometrical arguments, it is possible to reconstruct the shape of an internal structure from two orthogonal views. As with optical images of the external surface, the labour of measuring and calculating sufficient points is enormous, but the advent of digital radiology, especially of image-subtraction techniques, makes this practical.

In digital radiology, X-rays leaving the body fall on an image-intensifying screen and are converted to a picture than can be read directly by a television camera. Once the image is in digital form it can be enhanced, manipulated, stored and retrieved, in many ways. Perhaps most importantly, it can be subtracted from a previous image, leaving a picture of the difference between the two. This technique is sufficiently sensitive to provide images of the pulmonary circulation after quite small amounts of contrast medium have been injected into a peripheral vein (obviating the need for right-heart catheterization).

It is interesting to consider what can be learned from orthogonal views of bronchial or pulmonary arterial trees (Fig. 13). In principle, the position of each node (branching point) can be determined precisely. However, because twigs near to the image-trapping screen cast smaller shadows than those of the same size but further away, optical distortions have to be accounted for before this can be done. Once this is achieved, the x, y and z coordinates of each node can be calculated and the length of each twig determined. Since the width of the twig can be corrected for distortion and calculated in the same manner, the volume of each element can also be determined. We have written a program that does this automatically and have tested it on orthogonal images of a model tree consisting of 20 branches, forming five generations. Diameters were estimated at the mid-points of the images of each branch. The model displaced 121 ml of water. The program calculated its volume at 114 ml. The missing 7 ml represent nodal swellings that were ignored. More frequent sampling of diameters would overcome this.

The size, shape and position of each element can be compared with normal values, or with those of the same tree at another time, for example at an early stage in the invasion by contrast medium, in order to get regional blood flow, or before and after a deep breath. In that case, the motion of each node can be calculated and the volume, and therefore the change in volume, of each space contained by four neighbouring nodes can be determined, providing a means of measuring regional ventilation at segmental or subsegmental level.

All the techniques mentioned here, whether they are optical or radiographic, depend simply on applying elementary trigonometry to a large number of points. In the past this would have been extremely tedious to do. It is made practical by the advent of small, cheap computers. Over the next few years, the techniques are likely to contribute much to our understanding of the lung.

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LUNG FUNCTION IN YOUNG ADULTS WITH CYSTIC FIBROSIS

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Summary

Pulmonary function tests have been carried out on eight adults with cystic fibrosis. There were statistically significant correlations between the severity of the patient's clinical state as assessed by the Shwachman score and TLco, TLC and VC. In addition the RV/TLC ratio increased with increasing clinical severity. There were no significant correlations between clinical severity and other measurements of lung function such as FEV_1, PEFR, RV or Pco_2. Serial studies indicated that the TLco falls with increasing clinical severity of the disease. It is suggested that the objective measurements of pulmonary function should be included in any future 'scoring' system used to assess the severity of cystic fibrosis and that measurements of the single-breath TLco might be one of the more discriminant tests.

INTRODUCTION

Increasing numbers of patients with cystic fibrosis are surviving beyond adolescence into adult life and the chest physician is therefore likely to encounter young adults with advanced respiratory disease. Several authors have looked at pulmonary function in patients of all ages with cystic fibrosis (Beier et al. 1966; Featherby et al. 1969; Godfrey & Mearns, 1971; Corey et al. 1976). This study describes the changes in lung function in young adults with cystic fibrosis and examines their value in assessing the severity of the disease.

Materials and Methods

In the past four years, eight young adults with cystic fibrosis have been referred to the chest department at The London Hospital. In each case the diagnosis had been established at an early age on the basis of the clinical picture and an elevated sweat sodium concentration.

Each patient has been seen regularly and has had lung function tests performed on more than one occasion. Measurements were made of peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and Pco_2 (rebreathing method). Improvement of PEFR, FEV_1 or FVC was measured 10 minutes after inhalation of isoprenaline sulphate 160 μg. The transfer factor of the lungs for carbon monoxide (TLco) was estimated by the single-breath method of Ogilvie et al. (1957) The transfer coefficient (Kco) was calculated by the method of McGrath and Thompson (1959). Lung volumes were measured by helium dilution. The methods used for these tests have been described by Hughes and Empey (1972) and the predicted normal values were those of Cotes (1975).

With the exception of J. B. the results reported represent the most recent measurements of lung function, when the patients were relatively well and were free of infective exacerbations. In the case of J.B., her latest lung function had deteriorated to such an extent that we were unable to measure gas transfer by the single breath method; so that the results given refer to September 1978.

All patients were assessed clinically and had regular chest radiographs and frequent examinations of sputum. The severity of the disease at the time of pulmonary function testing was quantified according to the grading system of Shwachman and Kulczycki (1958). This requires the assessment of four features of the patient's illness, namely general activity, clinical findings, nutritional status and chest radiographic appearance. Each category is marked out a maximum of 25 and the Shwachman score is derived by adding these together. Thus with a score of 86–100 the clinical grade is considered 'excellent', 71–85 'good', 56–70 'mild', 41–55 'moderate' and <40 'severe'.

Table I. Clinical features of eight young adults with cystic fibrosis

Patient	*Age*	*Sex*	*Shwachman score*	*Additional clinical features*
A.O.	17	M	27	Diabetes
R.S.	18	M	56	Portal hypertension with oesophageal varices
J.B.	18	F	58	—
I.C.	20	M	60	Diabetes
D.C.	22	M	64	Diabetes
P.M.	22	F	78	—
K.L.	20	M	85	—
K.W.	20	F	91	—

RESULTS

Clinical features together with Shwachman score and grade of severity are outlined in Table I. Patients are listed in order of severity of their disease and range from A.O. who had severe pulmonary involvement and who died in respiratory failure, to K.W., who is sufficiently fit to compete in regional athletic competitions; R.S. has hepatosplenomegaly and portal hypertension which has caused severe gastrointestinal bleeding from oesophageal varices on two occasions. *Pseudomonas aeruginosa* was repeatedly cultured from the sputa of all but the least affected patients and often persisted in spite of courses of aminoglycoside antibiotics given systemically (Hughes & Russell 1981). A.O., I.C. and D.C. developed diabetes mellitus but control has not proved a problem. At the time of pulmonary function testing, all patients, with the exception of A.O. and R.S., were able to maintain a full-time job or student career.

Pulmonary function tests

The results of pulmonary function tests together with Shwachman score, are given in Table II. With the exception of K.L., all subjects showed evidence of airways obstruction (mean $FEV_1/FVC = 55\%$). The more severely affected patients tended to have a mixed pattern of obstruction and restriction (e.g. A.O. and J.B.). $P\text{CO}_2$ was elevated only in the most severely affected patient. Reduction of TLco below 75% of predicted normal was seen only in those patients with the more advanced disease. Kco was normal in all but R.S.

Table II. Lung function in eight young adults with cystic fibrosis

Patient	*Shwachman score*	VC	FEV_1	FEV_1 /FVC (%)	RV	TLC	RV/ TLC (%)	TLco	Kco	PEFR	$P\mathrm{co}_2$ (kPa)
A.O.	27	51	35	55	137	59	55	38	76	60	6.78
R.S.	56	86	56	54	113	94	31	66	61	66	4.85
J.B.	58	61	52	74	115	70	45	55	85	65	6.25
I.C.	60	46	15	28	137	72	47	60	111	31	5.66
D.C.	64	57	20	29	162	90	45	53	93	34	5.03
P.M.	78	91	66	60	127	105	37	80	103	92	5.67
K.L.	85	84	72	71	104	89	30	90	92	83	5.61
K.W.	91	104	83	66	109	104	32	107	108	87	5.85
Mean		72.5	50	55	125	85	40.0	68.0	92.5	65	5.71
(± SEM)		(±8.0)	(±9.0)	(±6.5)	(±7.0)	(±6.0)	(±3.5)	(±8.5)	(±5.5)	(±8.5)	(0.233)

Results are expressed as percentage of predicted normal except where indicated.

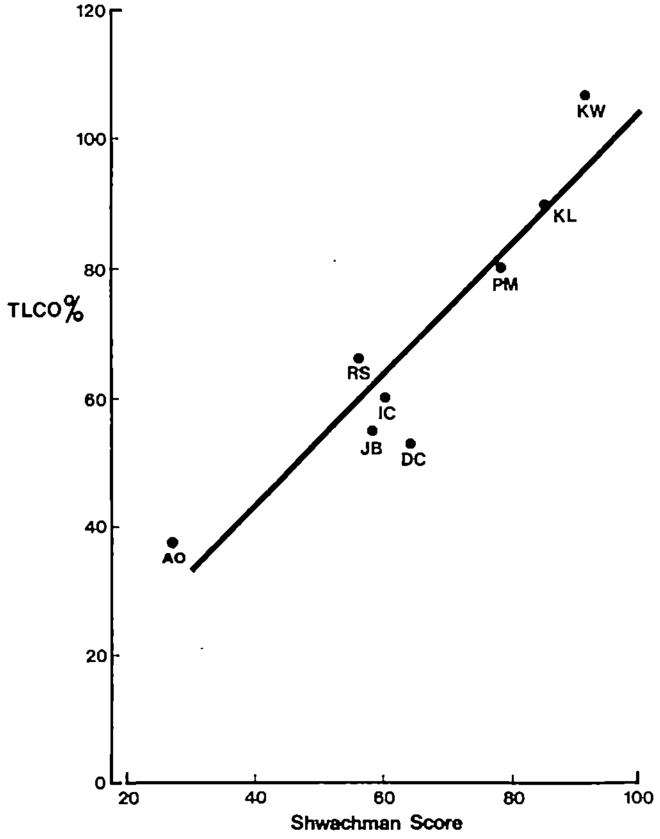

Fig. 1. The relationship between TLco (% predicted normal) and Shwachman score

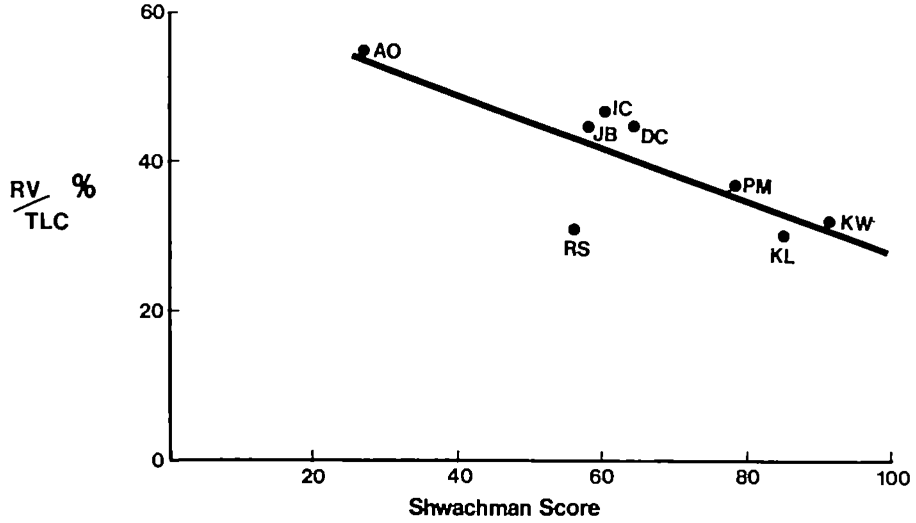

Fig. 2. The relationship between increasing RV/TLC% and diminishing Shwachman score

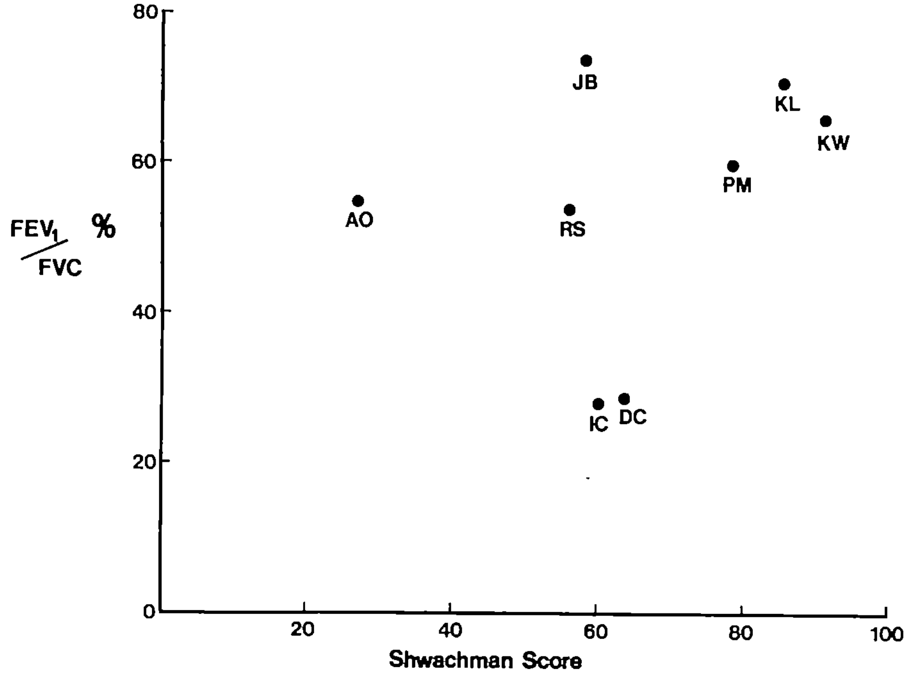

Fig. 3. The relationship between FEV1/FVC% and Shwachman score

Table III. Correlation of Shwachman score with pulmonary function measurements in eight young adults with cystic fibrosis

Test	*Correlation coefficient*	*Significance*
TLco	(+) 0.923	$P<0.01$
TLC	(+) 0.812	$P<0.02$
TV/TLC	(−) 0.789	$P<0.05$
VC	(+) 0.735	$P<0.05$
FEV$_1$	(+) 0.639	NS
Kco	(+) 0.637	NS
PEFR	(+) 0.515	NS
RV	(−) 0.436	NS
$P\mathrm{co}_2$	(−) 0.397	NS
FEV$_1$/FVC	(+) 0.285	NS

NS = not significant

The relationship between Shwachman scores and tests of lung function are shown in Figs 1, 2 and 3. There were significant direct correlations between the Shwachman score and TLco (Fig. 1), TLC and vital capacity. The inverse correlation between Shwachman score and RV/TLC% was also of significance (Fig. 2). The correlation was best for TLco (Table III). There were no statistically significant correlations between Shwachman score and other parameters of lung function, such as FEV$_1$, FEV$_1$/FVC% (Fig. 3), PEFR, RV, $P\mathrm{co}_2$ and Kco. Serial lung function tests performed on I.C. over a period of three and a quarter years are shown in Table IV. Serial decline in transfer factor in A.O., R.S., J.B. and I.C. is shown in Fig. 4.

Table IV. Serial lung function of I.C.

	December 1976 (*Age 17*)	*April* 1978 (*Age 18*)	*February* 1980 (*Age 20*)	*March* 1980 (*Age 20*)
VC (litres)	3.40	3.50	1.54	2.05
FEV$_1$ (litres)	1.80	1.90	0.60	0.57
FEV$_1$/FVC(%)	53	54	39	28
PEFR (litres/minute)	310	360	175	180
VC (litres)	3.75	4.1	2.06	2.24
FRC (litres)	3.45	3.55	2.05	2.26
RV (litres)	2.20	2.25	1.67	1.97
TLC (litres)	5.95	6.35	3.75	4.21
RV/TLC(%)	37	35	45	47
TLco (mmol/m/kPa)	8.04	7.37	6.78	6.29
Kco	1.89	1.93	2.40	2.16
$P\mathrm{co}_2$ (kPa)	5.9	5.5	5.62	5.66

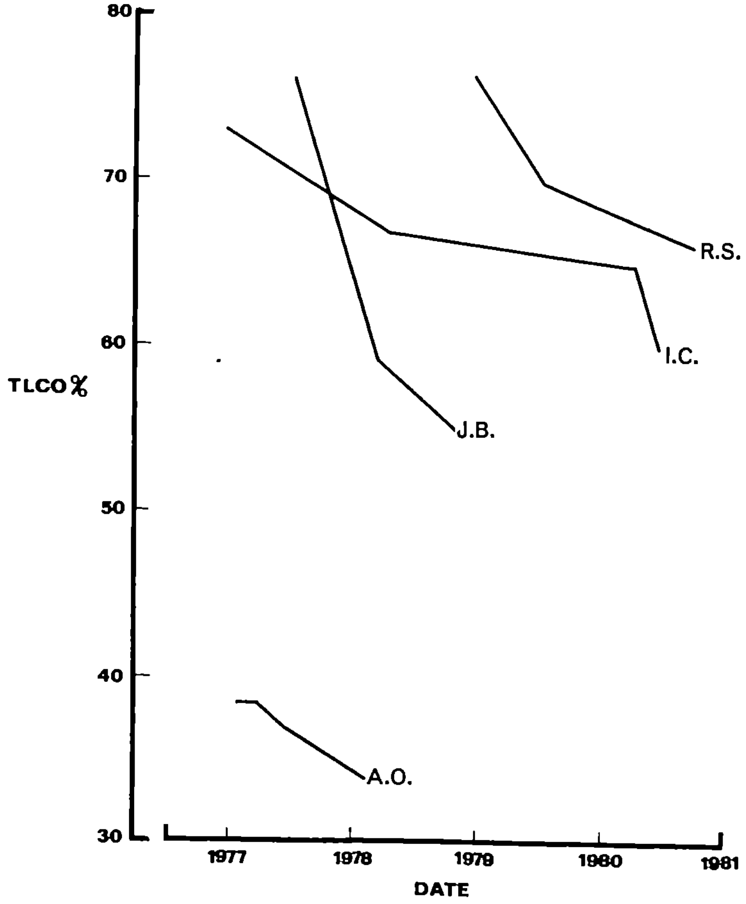

Fig. 4. Serial decline of TLco (% predicted normal)

Discussion

Overall, those with the lowest clinical score had the worst lung function. Airways obstruction was present in all but one subject and this finding is in agreement with other studies (West et al 1954; Cook et al. 1959; Beier et al. 1966). However, there was no significant correlation between either FEV_1 or $FEV_1/FVC\%$ and the clinical severity of the illness. This contrasts with the findings of Godfrey and Mearns (1971) who demonstrated a linear relationship between FEV_1 and clinical severity in patients of five to 21 years of age; similar observations have been made by Mitchell-Heggs et al. (1976) studying adolescents and young adults. We were able to show significant correlation between increasing RV/TLC% and increasing severity of disease, confirming the findings of Beier et al. (1966) with patients aged from eight to 18 years.

Although airflow obstruction was present in seven of our patients it did not conform to a uniform pattern. Firstly it may be quite severe in the presence of a high Shwachman score and in patients with a good exercise tolerance. This is well illustrated by I.C., who, despite an FEV_1 of 15% of predicted normal and an FEV_1/FVC of 28%, was able to maintain a place in his univeristy badminton first team and who regularly indulges in other sporting activities. Secondly, the presence of significant reversibility after a bronchodilator aerosol varied considerably, not only between patients but in the same patient on different occasions. For example, D.C. on three consecutive occasions showed changes in FEV_1 of +5%, +19% and −2% after a bronchodilator aerosol. R.S. and I.C. have shown similar variable responses to inhaled isoprenaline, but the remainder have never shown significant reversibility of FEV_1 or PEFR. Mitchell et al. (1978) found that bronchial hyperreactivity was a feature of patients with cystic fibrosis and was more marked in those with poorer lung function. Bronchial hyperreactivity after respiratory tract infection may explain the inconsistent reversibility seen in some of our patients.

Although airways obstruction was a prominent feature in our patients, there was no uniform pattern of disturbance and some patients (e.g. J.B.) showed a mixed pattern of restriction and obstruction. There was a significant inverse correlation between both TLC and VC and severity of the disease, though TLC was markedly reduced in only one patient who was also the most ill. These findings are similar to those of Beier et al. (1966) who also measured thoracic gas volume by the body plethysmograph and found this to be normal or raised in all their subjects, suggesting that there might be considerable gas-trapping in those with a reduced TLC as measured by helium dilution.

The most significant correlation was that between deterioration in TLco and increasing clinical severity of disease. Previous studies have produced conflicting results with regard to transfer factor. Beier et al. (1966), working with children and adolescents, found that TLco (single-breath method) was normal in all in whom it was measured (Shwachman scores ranging from 20 to 95). Keens et al. (1979) found that TLco (single-breath method) was consistently raised in 17 patients (aged nine to 24 years) with cystic fibrosis but did not comment on their clinical severity. Conversely, Goldring et al. (1964) reported reduced values for TLco (steady-state method) in 12 of 14 patients. Featherby et al. (1969) found a similar reduction in 51 of 126 studies on 80 patients (five of them over 20 years old) but they did not attempt to correlate this with clinical severity. Godfrey and Mearns (1971) found a reduction is steady-state TLco with increasing disease severity in 41 patients (aged five to 21 years) and this reduction became more marked in the more severely affected patients. Mitchell-Heggs et al. (1976) suggested that gas transfer was a useful measure of functional deterioration in those most severely affected patients, but did not state their method, nor did they make the measurement in all their patients.

Transfer coefficient (Kco) was above 75% of predicted normal in seven of our patients but was not significantly correlated with clinical severity. This suggests that, in those patients with a reduced TLco, the ventilated areas of the lung are comparatively normal and that the fall in TLco may reflect a decrease in accessible alveolar volume rather than impaired gas transfer.

$P\text{co}_2$ was elevated in only one patient who was also the most severely affected and who subsequently died in respiratory failure. This confirms the findings of Mitchell-Heggs et al. (1976) that a rise in $P\text{co}_2$ is a late event. No correlation was found between the severity of disease and $P\text{co}_2$ for the group as a whole.

Serial lung function measurements of I.C. (Table IV) show a decline in most parameters over a period of three and a quarter years. Airways obstruction, though present in 1976, became more prominent with a marked reduction in FEV_1 and FEV% and elevation of

RV/TLC ratio. There is some evidence of increasing restriction also, with a fall in VC and TLC. There was a progressive fall in TLco over this period. Clinically, although the patient has maintained a high degree of general activity, there has been increased sputum production and more frequent infective exacerbations for the past two years. Corey et al. (1976) report an exponential decline in FVC, FEV_1, $FEV/FEV_1\%$ and mean forced expiratory flow during the middle half of the FVC, in about three-quarters of their patients over a period of five to seven years. They did not correlate this with disease severity. From our own observations there appears to be a marked deterioration in serial lung function measurements only in those patients with more clinically severe disease, as typified by I.C. In particular transfer factor declines progressively in those patients with the lowest Shwachman scores (Fig. 4). In the remainder transfer factor has remained stable.

Previous grading systems have paid little attention to measurement of lung function and this may be because survival beyond childhood was unusual and it may be impractical to perform these tests on children. From our small group of patients it appears that, of the tests performed, a reduced TLco correlates best with the clinical severity of cystic fibrosis as measured by the Shwachman grading system. The criteria used for assessing disease severity are largely subjective and therefore prone to variation between observers. It seems reasonable to incorporate more objective observations into future grading systems and our results suggest that TLco is a useful guide to disease severity and might find a place in future scoring methods. However, studies on a larger group of patients and for a longer period of time are needed to determine whether long-term changes in TLco match those in clinical severity and to observe changes in other measurements of lung function.

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THE INFLUENCE OF LUNG VOLUME ON GAS TRANSFER IN SCOLIOSIS

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Summary

Single-breath carbon monoxide transfer factor (DLco) and diffusion coefficient (Kco) have been compared with vital capacity and total lung capacity in 119 subjects with scoliosis, 74 with idiopathic scoliosis, 32 with congenital osteogenic scoliosis and 13 with paralytic scoliosis. In each group mean values of DLco were below, and for Kco above, predicted values. Furthermore, in each group, DLco was correlated with lung volume and Kco inversely correlated with lung volume. The reduction in DLco is probably due to the reduction in the total alveolar surface area and the increased values for Kco probably result from an increase in pulmonary capillary blood volume per unit alveolar volume at low lung volumes.

INTRODUCTION

The carbon monoxide transfer factor (DLco) is frequently reduced below predicted values in patients with scoliosis (Prime 1965, 1977; Weber et al. 1975). Prime (1977) demonstrated that when DLco was corrected for the volume of lung available for gas transfer, and the diffusion coefficient (Kco) thereby derived, values in excess of predicted were obtained. Denison et al. (1980) and Siegler (1980) have since confirmed this finding. A further, more clinically detailed, analysis forms the basis of this present study. Changes in DLco and Kco have been studied in relation to changes in lung volume in 119 patients with scoliosis.

Patients and Methods

The results of routine lung function studies of all patients attending the Scoliosis Clinic at Brompton Hospital during the six-month period ending December 1979 have been reviewed. Cigarette smokers and patients with lung conditions unrelated to scoliosis, e.g. asthma or chronic bronchitis, have been excluded. Total lung capacity (TLC) was measured by body-box plethysmography. The carbon monoxide transfer factor (DLco) was measured by a standard single-breath technique and was related to the volume of lung available for gas transfer to obtain the diffusion coefficient (Kco). Vital capacity (VC) was obtained by simple spirometry. For the purpose of data analysis, values of DLco, Kco, TLC and VC have all been expressed as a percentage of the mean predicted value for age, height and sex (Cotes 1975). Predictions of normal values for pulmonary physiological variables are conventionally based on height, which is reduced in spinal curvature. No attempt to estimate the 'uncoiled height' of a scoliotic patient, including work from this unit by Prime and Zorab (1969), has been entirely satisfactory. Estimations from arm-span and tibial length have been attempted and work from this unit has previously used values based on height, but predicted values in this report are based on arm-span. Mean results are presented as mean (±1 SD) of predicted values of Cotes (1975).

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The patients have been divided into three groups on the basis of the aetiology of their spinal deformity:

1. Idiopathic scoliosis, including infantile, juvenile and adolescent types.
2. Congenital osteogenic scoliosis.
3. Paralytic scoliosis following poliomyelitis.

RESULTS

A total of 119 patients were available for analysis. Details of the patients are shown in Table I and the results of lung function tests in Table II.

Figs 1–6 show the correlations between the measurements of gas transfer and both VC and TLC for each of the three groups of patients. In each group, there is a statistically significant correlation between DLco and lung volumes, and a significant inverse correlation between Kco and lung volumes.

Table I. Age, sex and degree of scoliosis of subject studied

	Idiopathic	*Osteogenic*	*Paralytic*
Total number	74	32	13
Number who had spinal fusion	50	10	10
Mean age (years ± 1 SD)	26.4±9.5	17.8±6.9	30.5±7.9
Male/Female	20/54	20/12	6/7
Mean Cobb angle (degrees ± 1 SD)	76.4±35.1	79.1±36.4	85.1±39±1

Table II. Results of lung function tests (means of each group ± 1 SD)

	Idiopathic	*Osteogenic*	*Paralytic*
VC	62.5±20.4	57.5±24.3	51.0±20.9
TLC	70.2±19.5	68.3±24.4	59.3±20.9
DLco	70.0±15.7	71.4±23.4	60.8±19.2
Kco	115.5±25.4	121.7±18.1	118.2±19.7

DISCUSSION

This study confirms the findings of Prime (1965, 1977) of reduction in DLco and increase in Kco in patients with scoliosis, and demonstates a correlation between values for DLco and for lung volume expressed as VC and TLC It is most likely that the reduction in DLco is due to a reduction in the total area of the alveolar capillary membrane as a result of a low lung volume.

Bergofsky (1979) measured the diffusing capacity for oxygen (DLo_2) in a small group of scoliotic subjects. The value for DLo_2 fell progressively as the degree of spinal deformity and the respiratory disability increased. When corrected for lung volume, however, values within the predicted range were obtained, except in patients with carbon dioxide

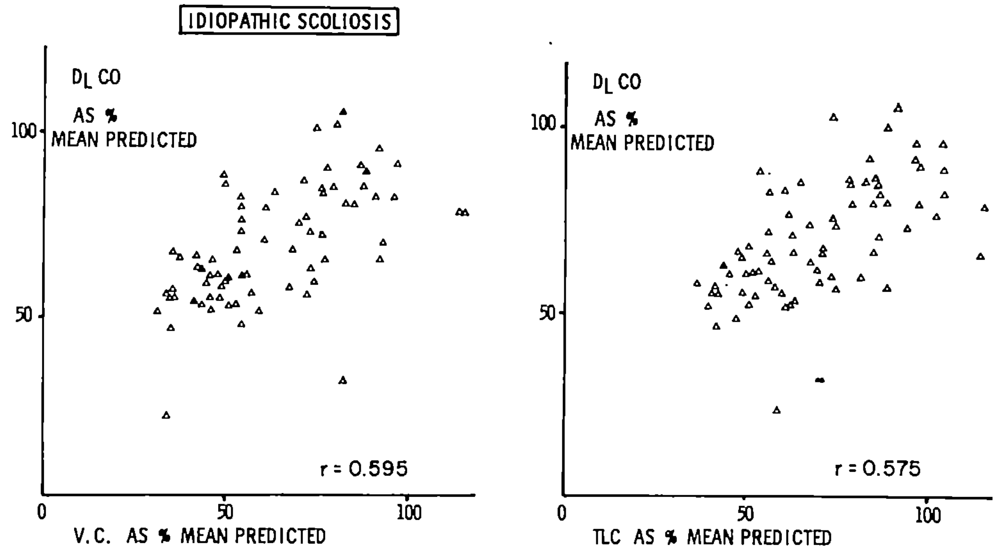

Fig. 1. DLco and lung volume in idiopathic scoliosis. r = linear correlation coefficient

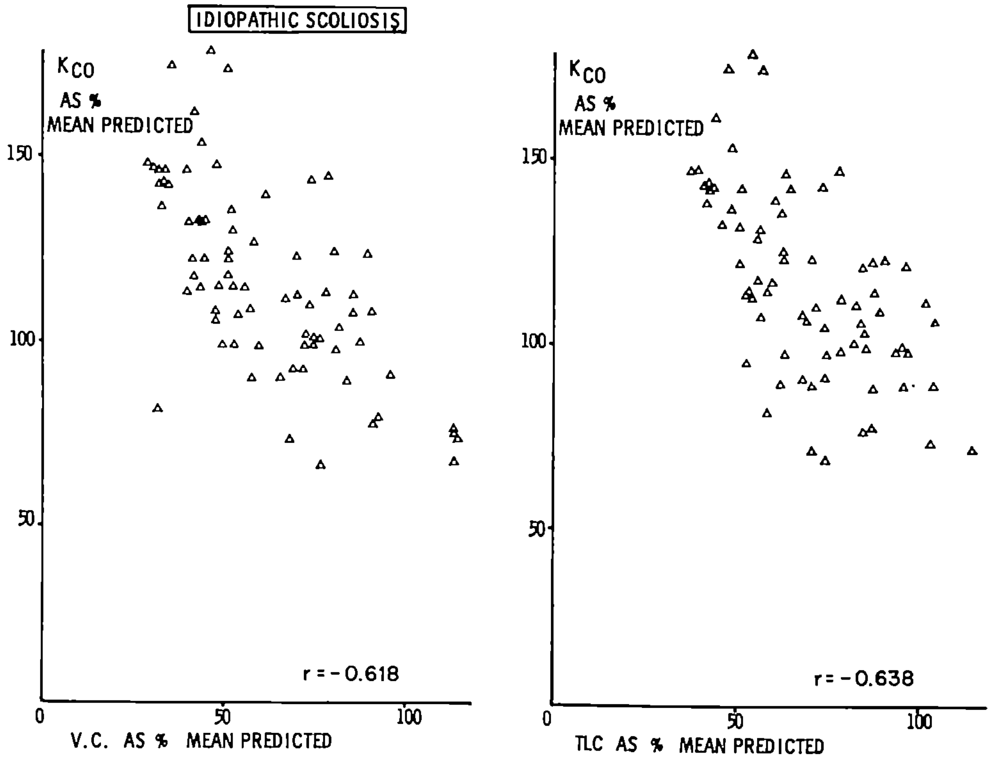

Fig. 2. KCo and lung volume in idiopathic scoliosis. r = linear correlation coefficient

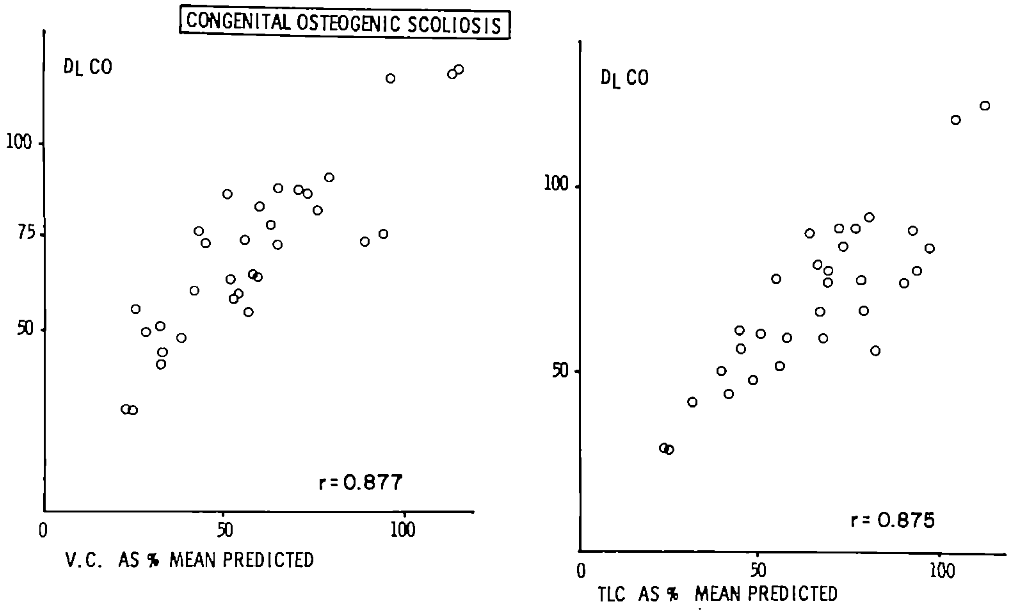

Fig. 3. DLco and lung volume in congenital osteogenic scoliosis. r = linear correlation coefficient

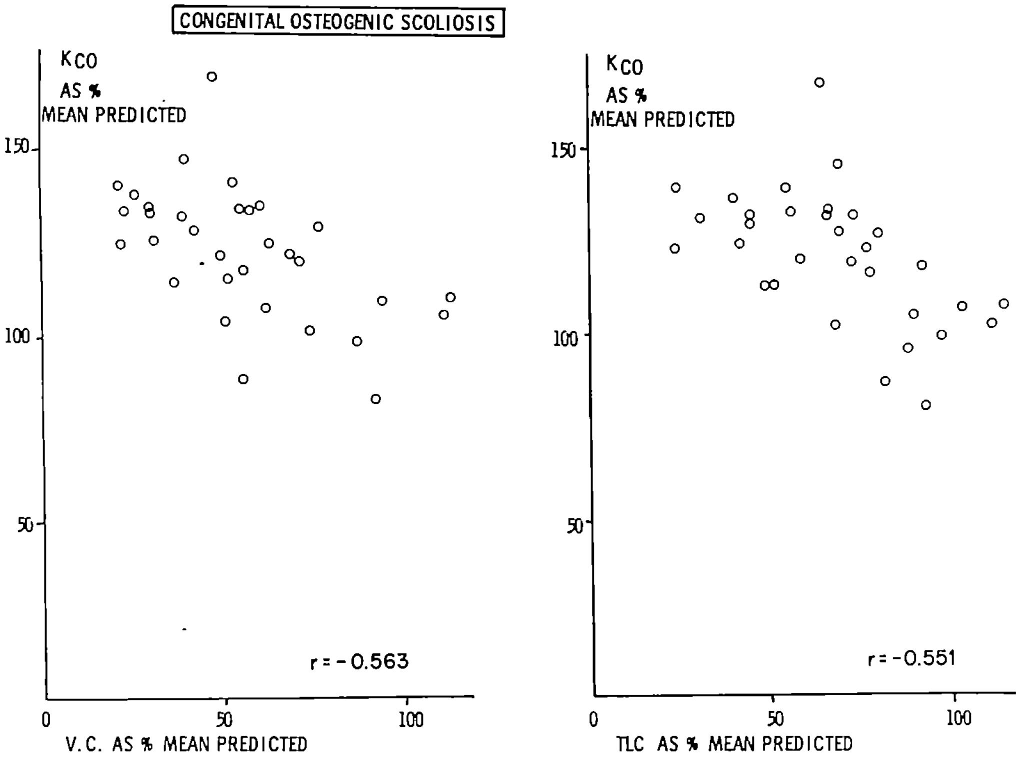

Fig. 4. Kco and lung volume in congenital osteogenic scoliosis. r = linear correlation coefficient

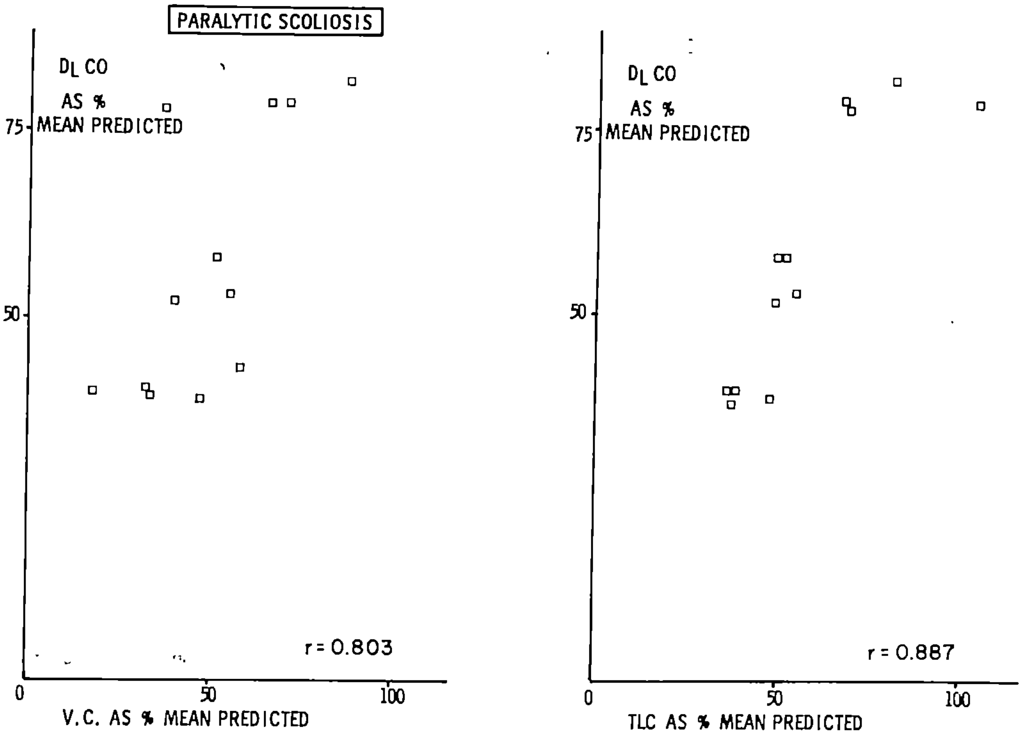

Fig. 5. DLco and lung volume in paralytic scoliosis. r = linear correlation coefficient

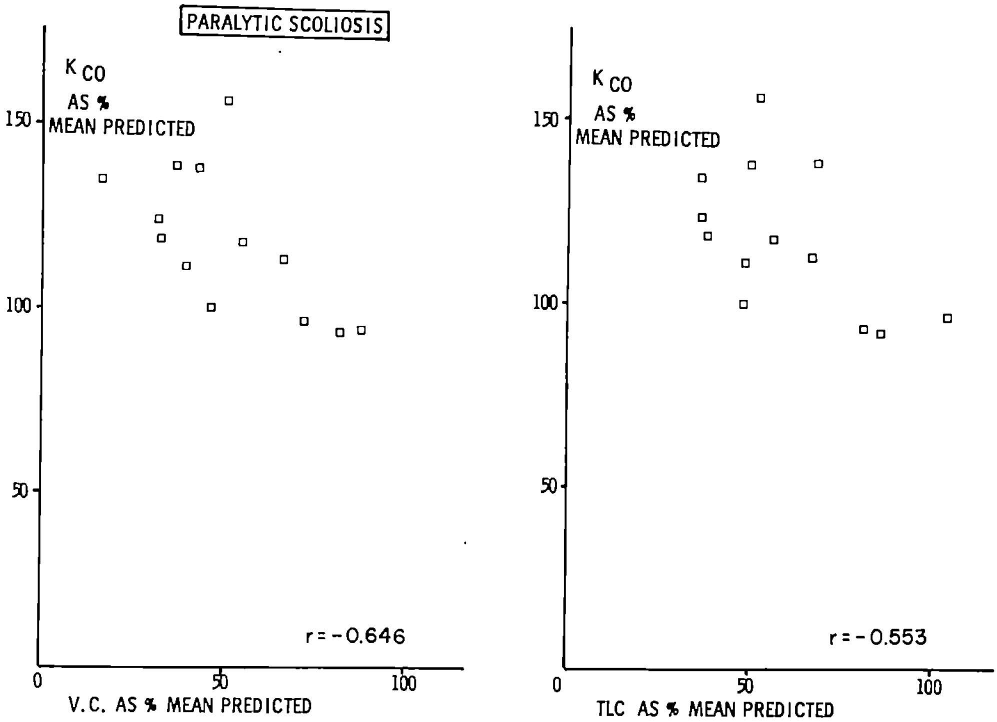

Fig. 6. Kco and lung volume in paralytic scoliosis. r = linear correlation coefficient

retention. Bergofsky extrapolated that with increasing severity of deformity and increasing age, progressive ventilation–perfusion mismatching would lead ultimately to gross alveolar hypoventilation and cor pulmonale.

Prime (1977) was the first to report values of Kco in excess of predicted in scoliosis. Weber et al. (1975) had earlier expressed values for diffusing capacity in terms of lung volume as DL/FRC and obtained normal values. The Kco may be regarded as representing the performance of the ventilated parts of the lung in terms of gas transfer, irrespective of their size. Lipscomb et al. (1978) suggested that Kco might be useful in interpreting abnormalities of DLco. Thus in emphysema, DLco and Kco are both reduced, whereas in asthma, although DLco may be reduced due to uneven gas distribution, Kco is usually normal or above normal. Lipscomb et al. (1978) studied 27 patients in whom high values of Kco had been obtained, two thirds of whom had documented episodes of intrapulmonary haemorrhage. The remaining nine patients with high Kco values had a variety of conditions (not including spinal deformity) in none of which a high Kco had been previously reported. In order to ascertain whether high Kco values could be explained simply on the basis of reduced lung volumes (in all patients, VC was significantly reduced) Kco was measured in six normal non-smokers at different lung volumes. Although Kco as a percentage of predicted increased exponentially as lung volume fell the authors concluded that changes in lung volume could not completely explain high Kco values and that an increase in capillary blood volume per unit alveolar volume at lower lung volumes could be partly responsible.

The changes in alveolar geometry and alveolar–capillary blood volume during normal lung inflation and deflation may help to explain the rise in Kco as lung volume falls. Weibel (1973) demonstrated by electron microscopy that the thickness of the membrane separating alveolar gas and capillary blood is maintained constant at all physiological lung volumes. During deflation the thicker elements of the blood–gas barrier are displaced away from the thinnest portion of the alveolar membrane. Thus changes in the membrane component of the transfer factor are unlikely to account for changes in Kco. Glazier et al. (1969) showed in isolated greyhound lungs that the total pulmonary capillary blood volume is approximately constant at all lung volumes and thus the ratio of capillary blood volume to alveolar gas volume rises as lung volume is reduced. Hence Kco will rise at lower lung volumes. This provides a theoretical basis for the high Kco values in scoliotics with small lung volumes. Lipscomb et al. (1978) confirmed the finding of previous studies that in normal subjects whereas the membrane component of the transfer factor and the total capillary blood volume do not change with lung volume, the ratio of capillary blood volume to alveolar volume virtually doubles during deflation from TLC to FRC.

In pathological terms Reid (1969) showed that both failure of development of new alveoli and atrophy of those already formed led to reduction in lung volumes in scoliosis. The range of alveolar size may be greater than normal. Furthermore, the development of blood vessels does not necessarily parallel that of the alveoli and abnormalities of alveoli and blood vessels are irregularly distributed within lobes or lungs. These abnormalities could further help to explain changes in gas transfer in the lung in scoliosis.

Prime (1965) pointed out that in scoliosis the lungs are small but in terms of gas exchange are functioning at a high level of efficiency. Thus, the loss of any functioning lung, e.g. during an acute infective episode, may have very serious consequences.

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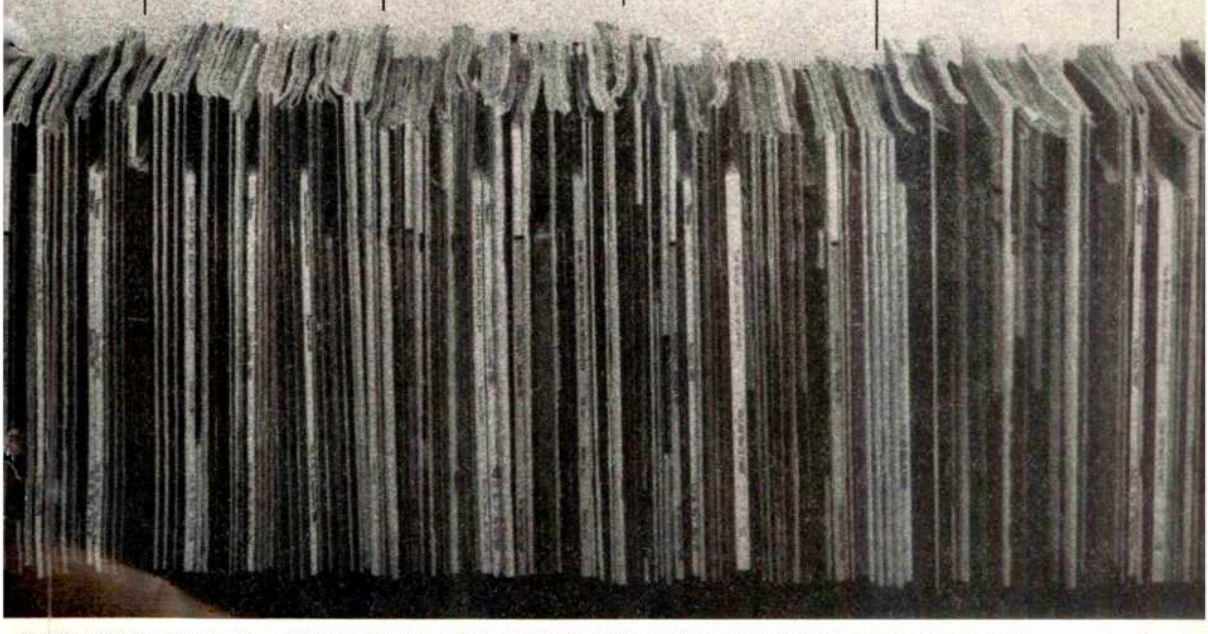

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Br. J. Dis. Chest (1982) *76*, 51

DIURNAL VARIATION OF AIR AND HELIUM–OXYGEN FLOW–VOLUME CURVES IN ASTHMATIC CHILDREN

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Summary

In order to assess diurnal variation of flow–volume curves and to determine whether small airways are involved in the diurnal variation of pulmonary function in asthmatic children, we studied eight asthmatics who were attending an asthma summer camp. Spirometry and maximal expiratory flow–volume curves with air and a helium-oxygen mixture were obtained in the morning and afternoon over a 10-day period. We found that significant increases in maximal expiratory flows at all lung volumes occurred in the afternoon. However, the increase in flows with helium (helium response) was unchanged from morning to afternoon. These results suggest that both large and small airways are involved in the diurnal variation of pulmonary function in asthmatic children.

INTRODUCTION

Previous reports have documented a diurnal variation in pulmonary function with the lowest values occurring between midnight and 0600 hours. Pulmonary function then peaks in the afternoon and begins to fall in the late evening (Reinberg & Gervais 1972; Lewinsohn et al. 1960). These changes, in varying magnitude, have been demonstrated in adult patients with chronic obstructive lung disease (Hruby & Butler 1975; Connolly 1979), restrictive lung disease (Hruby & Butler 1975), asthma (Clark & Hetzel 1977) and normal individuals (Guberan et al. 1969; Walford et al. 1966). Parameters examined in these included FEV_1, peak expiratory flow rate, lung volumes and airway resistance, which were indicators of large airway function. Whether diurnal variation of pulmonary function occurs in the small airways has not been examined previously except in one study of adult asthmatics (Hetzel et al. 1977), and no such study has been published in asthmatic children.

In order to assess the pattern of diurnal variations of pulmonary function in asthmatic children, we performed spirometry and flow–volume curves with air and helium–oxygen twice daily in a group of moderately severe asthmatics attending an asthma summer camp. The following question was asked. Since large airway changes have been shown to occur in the diurnal variation, are the small airways also involved in the diurnal variation of pulmonary function in asthmatic children? We have previously reported that the pattern of forced expiratory flow limitation following a bronchial challenge with antigen or methacholine is consistent with large and small airway responses (Permutt & Menkes 1979), and unlike changes associated with age and smoking. However, whether similar responses through the day occur in asthmatic children is not known.

Material and Methods

Subjects

Five males and three females with perennial moderately severe asthma were studied twice each day (at 0800–0900 hours and at 1700–1830 hours) for 10 days while resident at an asthma summer camp. The mean age was 13.1 years, the mean weight percentile was 19.4 and the mean height percentile was 15.6. All subjects were taking theophylline every eight hours. In addition seven of eight subjects were taking oral β_2 agonists (metaproterenol or terbutaline), four of eight were taking inhaled beclomethasone and three of eight disodium cromoglycate. There were no medication changes during the study period. Informed consent was obtained from all children and their parents.

Experimental procedure

Forced expiration was measured in the standing position using a 10 litre Steadwell's water sealed spirometer fitted with a linear potentiometer. The volume data were collected with a microcomputer (model 8080, Santa Clara, CA) with a 12 bit analog-to-digital converter sampling at 120 times per second. Three forced expiratory manoeuvres were performed first with air. Then the subjects were asked to take three inspirations of a mixture containing 80% helium and 20% oxygen (He–O_2), and the forced expiratory manoeuvre was repeated. Forced expiration with He–O_2 was performed twice. The spirometric data were stored on magnetic tape and analysed at a later time.

In order to eliminate spurious volume points caused by electrical interference, volume–time relationships were processed by two passes through a digital filtering routine using the least-squares polynomial approximation (Dahlquist & Bjorck 1974). After digital smoothing, the best of the three air spirograms and the best of the two He–O_2 spirograms were used for determining forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC).

Maximal expiratory flow–volume (MEFV) curves were obtained by digital differentiation of the volume–time data. The best of the three air MEFV curves and the best of the two He–O_2 MEFV curves were used for determining the maximal expiratory flow ($\dot{V}_{max}$), and maximal expiratory flows at 75, 50 and 25% of vital capacity ($\dot{V}_{75}$, $\dot{V}_{50}$, $\dot{V}_{25}$). If the FVC of the best air and the best He–O_2 manoeuvres at any one sitting differed by more than 10%, the data were excluded from the analysis. This accounted for a 4% rejection of the data.

The degree of density dependence of maximal expiratory flow was assessed by calculating the ratio of $\dot{V}_{max}$ He–O_2 to $\dot{V}_{max}$ air at 50% of vital capacity ($\dot{V}_{50}$ He–O_2/air).

Serum theophylline levels were measured in duplicate from capillary specimens using the EMIT Theophylline Assay (Syva, Palo Alto, CA). Theophylline levels were done at the time of both the morning and afternoon studies on day one, and no subsequent dosage changes occurred during the study.

Statistical analysis

All values were expressed as the mean ± 1 SD. Statistical significance was assessed by the paired *t*-test. Statistical significance was accepted if $P < 0.05$.

RESULTS

Spirometry with air revealed a significantly higher mean FEV_1 and FVC in the afternoons. This trend was also present in the He-O_2 spirograms (Table I). Whereas the morning and afternoon FEV_1 with He-O_2 was consistently higher (9% and 7% respectively) than the FEV_1 with air alone, the FVC with He-O_2 did not differ from the FVC with air.

Table I. Diurnal variation of spirometry and maximal expiratory flows in subject breathing air and a He–O_2 mixture

	Morning	*Afternoon*	*Significance level*
Forced expiration with air			
FEV_1 (litres)	1.78±0.67	1.94±0.68	<0.005
FVC (litres)	2.42±0.70	2.51±0.65	<0.005
$\dot{V}_{max}$ (VC/sec)	1.91±0.38	2.02±0.40	<0.005
$\dot{V}_{75}$ (VC/sec)	1.19±0.38	1.37±0.42	<0.005
$\dot{V}_{50}$ (VC/sec)	0.65±0.22	0.72±0.23	<0.05
$\dot{V}_{25}$ (VC/sec)	0.31±0.14	0.35±0.15	<0.05
Forced expiration with He–O_2			
FEV_1 (litres)	1.94±0.74	2.08±0.75	<0.0001
FVC (litres)	2.45±0.71	2.55±0.68	<0.0001
$\dot{V}_{max}$ (VC/sec)	2.29±0.42	2.47±0.53	<0.0001
$\dot{V}_{75}$ (VC/sec)	1.57±0.55	1.80±0.56	<0.0001
$\dot{V}_{50}$ (VC/sec)	0.82±0.30	0.91±0.33	<0.005
$\dot{V}_{25}$ (VC/sec)	0.35±0.16	0.38±0.17	NS

Group mean ± 1 SD.

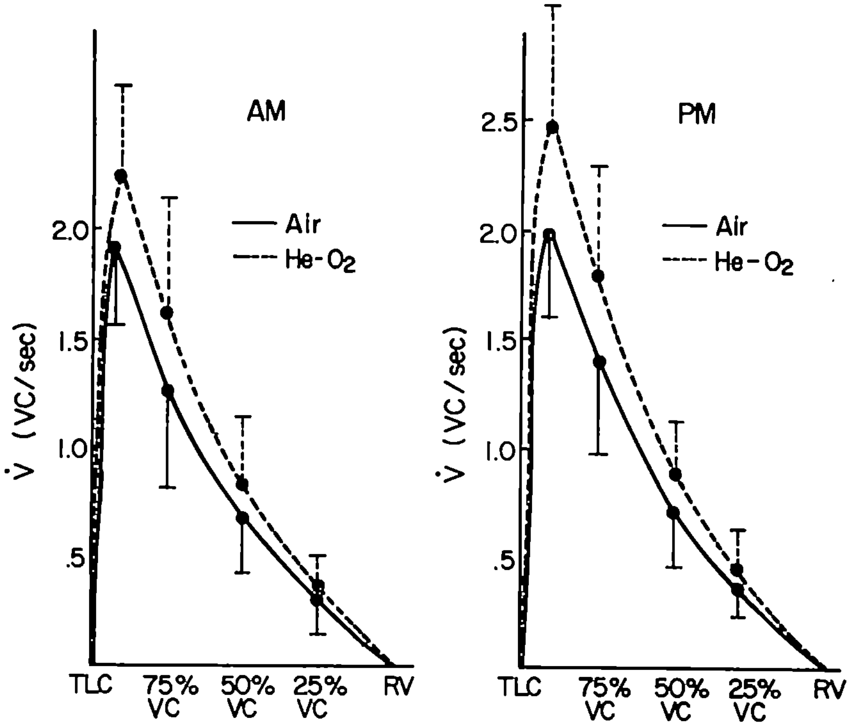

Fig. 1. Maximal expiratory flow–volume curves with air and He–O_2 constructed from group mean flow data and one standard deviation. The left-hand plot describes the helium response for mornings and the right-hand one that for afternoons. Expiratory flow ($\dot{V}$) in vital capacity per second (VC/sec) is plotted on the Y-axis and lung volume from TLC to RV, on the X-axis

Maximal expiratory flows were significantly higher in the afternoons for breathing both air and He-O_2 and these increases occurred at all lung volumes. Maximal expiratory flows were also significantly increased with He-O_2 as compared to air for both the mornings and afternoons (Fig. 1) When the ratio of $\dot{V}_{max}$ He-O_2 to $\dot{V}_{max}$ air at 50% of vital capacity ($\dot{V}_{50}$ He-O_2/air) was used to assess the degree of density dependence, we found that the mean group ratio was 1.29 in the morning and 1.31 in the afternoon. Moreover, none of the eight subjects, when examined individually, showed any change in the $\dot{V}_{50}$ He-O_2/air ratios (Table II). Three of the eight subjects consistently had a He-O_2 response of 20% or less (i.e. $\dot{V}_{50}$ He-O_2/air ratios less than 1.20). The remaining five subjects repeatedly demonstrated a response of 20% or greater and their $\dot{V}_{50}$ He-O_2/air ratios were greater than 1.20.

Three subjects experienced acute asthma attacks during the study. In the days immediately following the acute attacks, expiratory flows and volumes were diminished, but the diurnal variation was preserved.

The theophylline levels for mornings and afternoons were not significantly different (13.5 ± 3.2 mg/ml in the mornings and 15.1 ± 6.1 mg/ml in the afternoons).

Table II. Ratio of maximal expiratory flow at 50% of vital capacity with He–O_2 and air ($\dot{V}_{50}$ He–O_2/air)

Subject	*Morning*	*Afternoons*
1	1.33	1.39
2	1.26	1.26
3	1.53	1.54
4*	1.18	1.20
5*	1.08	1.10
6	1.26	1.24
7	1.49	1.50
8*	1.12	1.14
Group mean	1.29	1.31

Individual means over a 10 day period.
*Non-responder.

DISCUSSION

In this study we found significant diurnal changes of pulmonary function as measured by spirometry and flow–volume curves in chronic asthmatic children who were maintained with therapeutic serum theophylline levels and other anti-asthmatic drugs.

Results of MEFV data in the diurnal variation from this study allow us to examine mechanisms of expiratory flow limitation involved in the diurnal changes. We found that maximal expiratory flows increased the same proportion at all lung volumes. This was similar to Permutt and Menkes' finding that in allergic subjects after antigen challenge, the expiratory flows were diminished proportionally throughout forced expiration, with no change in the dispersion of transit times (Permutt & Menkes 1979). Similarly, in comparing the MEFV curves of asthmatic subjects to normals, Pride et al. (1967) noted that the maximal expiratory flows of the asthmatics decreased, but the shapes of the

MEFV curves were preserved, indicating that flows were not preferentially affected at any lung volume.

MEFV curves with He-O_2 have been used to assess the site of airflow limitation. Helium is less dense but more viscous than air. In normal subjects the resistance to forced expiratory flow is primarily due to turbulence and convective acceleration in the large airways. For normals, breathing a less dense gas such as helium will result in increased expiratory flow rates at nearly all lung volumes (Despas et al. 1972). In patients with small airway dysfunction, a larger component of resistance is related to obstruction in small airways. Since resistance in small airways is less dependent on gas density, flows do not increase as much with helium, especially at low lung volumes. According to the definition of Despas et al. (1972) individuals in whom the maximal expiratory flow at 50% of the vital capacity increases more than 20% with He-O_2 (i.e. $\dot{V}_{50}$ He-O_2/air > 1.20) are classified as responders. In this study, we found that five of the eight asthmatics were consistent responders during both the mornings and afternoons, suggesting that resistance in the large airways provided a major component to airflow limitation at all times in these subjects. The other three subjects were consistently non-responders, whether studied in the mornings or afternoons, suggesting that their predominant site of airflow limitation was in the small airways. In a group of adult asthmatics studied before and after induced bronchoconstriction, Chan-Yeung et al. (1976) found that the site of airway obstruction remained constant, as responders remained responders and non-responders were still non-responders before and after exercise or antigen challenge. They also noted that non-responders showed a greater obstructive defect. In our three asthmatic children who were non-responders, there was no correlation of helium response with the degree of airway obstruction, as compared to our five responders.

Finally, in assessing the site responsible for the diurnal variation of pulmonary function, we examined changes in the ratio of $\dot{V}_{50}$ He–O_2/air from mornings to afternoons. If the improvement of flows occurs because of changes in the large airways, the ratio should decrease. But if the improvement occurs because of changes in the small airways, the ratio should increase. Our findings indicated that the ratios were consistently unchanged in all of the subjects, suggesting that both large and small airways were involved in the diurnal improvement of pulmonary function. Hetzel et al. (1977) studied diurnal variation in adult asthmatics with He–O_2 MEFV curves and concluded that the calibre of both large and small airways decreased at night but that improvement was more complete in large airways during the day. Their conclusion was based on the finding of low airway conductance in the early morning with improvement in the afternoon. Changes in the $\dot{V}_{50}$ He–O_2/air ratio were not examined. Other studies focussing on the site of flow limitation in postexertional asthma have been reported with measurements of $\dot{V}_{50}$ He–O_2/air ratios (Benatar & Konig 1974; Mildon et al. 1974; McFadden et al. 1977). These ratios, before and after exercise challenge, were reported in both adults and children, but most subjects were studied only once or at most twice. Changes in the ratio were variable, and varying proportions of the subjects demonstrated an increase or decrease in this ratio. In contrast, our study showed no change in the $\dot{V}_{50}$ He–O_2/air ratio, and these results were based on studying the same subjects repeatedly over a 10-day period.

In summary, significant diurnal variations in FEV_1, FVC and maximal expiratory flows were demonstrated in a group of moderately severe asthmatic children who were maintained with therapeutic levels of theophylline. The increase in maximal expiratory flows from mornings to afternoons was similar at all lung volumes and the improvement of flows corresponding to the diurnal changes was consistent with changes in both the large and small airways.

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A CONTROLLED STUDY OF SLOW-RELEASE THEOPHYLLINE AND AMINOPHYLLINE IN PATIENTS WITH CHRONIC BRONCHITIS

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Summary

Twenty patients with chronic bronchitis who were also receiving β-agonist inhalers entered a single-blind cross-over study comparing slow-release aminophylline (Phyllocontin) 325 mg twice daily and slow-release theophylline (Rona-slophyllin) 250 mg twice daily with placebo. 16 subjects who completed the study showed no objective or subjective benefit with either active preparation. Eight of the 16 patients achieved plasma theophylline levels of greater than 10 μg/ml on each of the drugs but no benefit was found when this group was analysed separately.

INTRODUCTION

Bronchodilating drugs probably act by increasing cellular cyclic 3,5-AMP. β_2 adrenoceptor agonists achieve this by stimulation of the adenyl cyclase system, whereas theophylline and other methyl-xanthines act by inhibition of cyclic nucleotide phosphodiesterase which is responsible for conversion of cyclic 3,5-AMP to 5-AMP. Theophylline produces maximal bronchodilatation when plasma levels of 10–20 μg/ml are maintained (Turner-Warwick 1957) and oral theophylline preparations have been shown to relieve airways obstruction in asthmatics (Dyson & Campbell 1977; Hambleton et al. 1977; Tedders et al. 1976; Marlin et al. 1978). Bronchodilators are also frequently prescribed to dyspnoeic patients with chronic bronchitis but the benefit of oral methyl-xanthines in this disease has not been established. The present study was designed to investigate the effectiveness of two sustained-release methyl-xanthine preparations in relieving the airways obstruction of chronic bronchitics.

Patients and Methods

Twenty patients with chronic bronchitis who gave informed consent entered a single-blind, cross-over study. Besides fulfilling the standard M. R. C. criteria for bronchitis (Medical Research Council 1965), these patients showed 5–15% reversibility of airways obstruction after 200 μg of inhaled salbutamol. Oral bronchodilators were discontinued prior to the study and patients receiving corticosteroids were excluded. All other medications were continued unchanged and subjects spent two weeks each on placebo (one tablet twice daily), slow-release aminophylline (Phyllocontin) 325 mg twice daily (equivalent to 520 mg theophylline daily) and slow-release theophylline

250 mg twice daily (equivalent to 500 mg theophylline daily) in a random order. Placebo tablets differed in appearance from the slow-release preparations but patients did not know which was which.

At the first visit each patient was provided with a Mini-Wright peak flow meter, drugs for the first two-week period and a diary card. Throughout the study patients were allowed to use their sympathomimetic inhalers to a maximum of two puffs four-hourly as required, in addition to the trial tablets, and recorded the number of puffs/day on the diary card. At the end of each week of treatment, subjects described any side-effects noticed and answered the question 'How has the treatment helped you during this week?' The answer was graded: not at all (score 0), slightly (score 1) or greatly (score 2). A daily symptom score was also recorded with regard to wheeze, cough and chest tightness, each of which was graded according to severity: none (score 0), slight (score 1), moderate (score 2), severe (score 3) or very severe (score 4).

Patients were seen at intervals of two weeks for six weeks. At each visit diary cards were collected, blood was taken for theophylline level and drugs for the following two weeks and a new diary card were issued.

Table I. Mean morning and evening PEFRs while on each treatment

	Morning PEFR (litres/mean)		*Evening PEFR* (litres/mean)	
Placebo *vs.* slow-release aminophylline	213 ± 17.5 227 ± 18.3	$P=0.58$	227 ± 18.4 231 ± 19.3	$P=0.8$
Placebo *vs.* slow-release theophylline	213 ± 17.5 224 ± 17.8	$P=0.64$	227 ± 18.4 228 ± 18.0	$P=0.95$
Slow-release aminophylline *vs.* slow-release theophylline	227 ± 18.3 224 ± 19.8	$P=0.82$	231 ± 19.3 228 ± 18.0	$P=0.92$

Mean ± SE.

RESULTS

Twenty patients (19 males) entered the study. Their mean age was 60 years (range 51–73) and all were smokers or ex-smokers. Four patients failed to complete the trial: one discontinued slow release theophylline because of persistent nausea, another continued to take other oral bronchodilator tablets throughout the study and two were suspected of poor compliance because of negligible theophylline levels after two weeks of active drug.

In the 16 patients who completed the study, the mean theophylline level was 8.7 μg/ml slow-release aminophylline and 8.2 μg/ml on slow-release theophylline. Eight patients achieved theophylline levels within the range 10–20 μg/ml on both drugs, with a mean of 11.7 μg/ml on slow-release aminophylline and 11.5 μg/ml on slow-release theophylline. No side effects were reported with either drug by the 16 patients completing the study.

Mean peak expiratory flow rates (PEFR) of individual patients were calculated for the final 10 days of each treatment period. Morning and evening PEFRs were calculated separately and the values on slow-release aminophylline and on slow-release theophylline were compared with each other and with placebo using paired sample Student's t-test (Table I). Mean percentage PEFRs were within 40–50% of the predicted normal values throughout the study. No significant improvement in morning or evening PEFR was found with either active drug. Separate analysis of the eight subjects with theophylline levels within the therapeutic range likewise revealed no benefit from either drug and PEFRs did not differ from those of the patients with theophylline levels of less than 10 μg/ml (Table II).

Inhaler usage did not differ significantly during the treatment periods: placebo period = 5.2 puffs/day (± 1.3 SE), slow-release aminophylline period = 4.4 puffs/day (± 0.98 SE) and slow-release theophylline period = 5.0 puffs/day (± 1.28 SE).

The patients' assessments of the treatments and their symptom scores for cough, wheeze and chest tightness were analysed using Wilcoxon's rank sum test and no benefit was found with either theophylline preparation. These observations applied equally to patients with theophylline levels within and below the therapeutic range.

Table II. Morning and evening PEFR while on each treatment in relation to plasma theophylline levels

	*Group A**		*Group B**	
	Morning PEFR (litres/min)	Evening PEFR (litres/min)	Morning PEFR (litres/min)	Evening PEFR (litres/min)
Placebo *vs* slow-release aminophylline	228 ± 24.0 239 ± 21.4 $P=0.74$	238 ± 27.4 241 ± 25.0 $P=0.93$	197 ± 26.1 214 ± 30.4 $P=0.68$	215 ± 25.7 220 ± 30.6 $P=0.9$
Placebo *vs.* slow-release theophylline	228 ± 24.0 234 ± 23.5 $P=0.86$	238 ± 27.4 240 ± 27.0 $P=0.96$	197 ± 26.1 207 ± 25.2 $P=0.78$	215 ± 25.7 216 ± 24.8 $P=0.98$
Slow-release aminophylline *vs.* slow-release theophylline	239 ± 21.4 234 ± 23.5 $P=0.88$	241 ± 25.0 240 ± 27.0 $P=0.98$	214 ± 30.4 207 ± 25.2 $P=0.87$	220 ± 30.6 216 ± 24.8 $P=0.92$

Mean ± SE.

* Group A = Eight patients with mean plasma theophylline level of 10–20 μg/ml (= 11.7 μg/ml on slow-release aminophylline and 11.5 μg/ml on slow-release theophylline). Group B = Eight patients with mean plasma theophylline levels below 10 μg/ml (= 6.6 μg/ml on slow-release aminophylline and 6.7 μg/ml on slow-release theophylline).

DISCUSSION

Oral methyl-xanthines are commonly prescribed to patients with chronic bronchitis who manifest minor improvement of airways obstruction after sympathomimetic agents. We found no therapeutic benefit from two slow-release methyl-xanthines in such patients, using dosages commonly prescribed in clinical practice. One half of our patients did not achieve therapeutic levels of theophylline with the dosages used but the other half, whose levels were greater than 10 μg/ml, also failed to derive subjective or objective improvement. None of our subjects had serum levels towards the upper limit of the therapeutic range and it may be that higher levels are necessary for benefit to occur (Addis et al. 1980). The complete lack of response in our patients makes this unlikely.

However, the patients took, on average, five puffs of a beta-agonist per day and it is possible that the limited reversibility in this disease was already attained with the beta-agonists, leaving no room for improvement by methyl-xanthines.

There was a notable lack of side effects in these bronchitic patients in comparison with studies using methyl-xanthines in adult asthmatic patients, where side effects have been reported in up to 70% of patients (Greening et al. 1979; Tinkleman et al. 1979; Trembath & Boobis 1979; Monie et al. 1981). This suggests either increased sensitivity of asthmatic patients to side-effects of methyl-xanthines or reduced sensitivity of bronchitics, or a combination of both factors.

The basic cost of one month's treatment with Phyllocontin (325 mg twice daily) is £4.88 and with Rona-slophyllin (250 mg twice daily) is £3.02. We have found no indication for prescription of either medication in these dosages to chronic bronchitics already using beta-agonist inhalers.

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COMPARISON OF TWICE DAILY ADMINISTRATION OF A NEW CORTICOSTEROID BUDESONIDE WITH BECLOMETHASONE DIPROPIONATE FOUR TIMES DAILY IN THE TREATMENT OF CHRONIC ASTHMA

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Summary

The efficacy and side-effects of a new corticosteroid aerosol, budesonide and beclomethasone dipropionate were assessed in 30 patients with chronic asthma in a double-blind cross-over study. Budesonide was administered, 200 μg twice daily, from a conventional pressurized aerosol with a tube spacer extension attached and beclomethasone was given via a conventional inhaler in the recommended four times daily dose of 100 μg, each treatment being administered for one month. No clinically significant differences were found between the two treatments and no significant side-effects were observed.

INTRODUCTION

Budesonide (16α,17α-22 R,S)-a propylmethylene-dioxypregna-1, 4-diene-11B,21-diol-3,20 dione) is a new, potent, non-halogenated corticosteroid which has been shown to possess a high degree of anti-inflammatory activity. Animal studies confirm that the compound has a high glucocorticoid effect with minimal mineralocorticoid effect (Astra Pharmaceuticals Ltd; Data on file). Topical application in the vasoconstrictor test of McKenzie shows that it is two to three times more potent than beclomethasone dipropionate (beclomethasone) with similar systemic effects (Johansson et al. 1981), suggesting that budesonide administered by inhalation would be an effective treatment for bronchial asthma. This study was designed, therefore, to assess the efficacy of budesonide in patients with chronic asthma requiring treatment with an inhaled corticosteroid preparation.

The high degree of topical activity of budesonide suggested that it could be effective when given twice daily and hence it was decided to compare twice daily budesonide with beclomethasone given in the conventional four times daily dose schedule. Since the interposition of a tube spacer between the inhaler and the mouthpiece reduces oro-pharyngeal deposition of drugs (Moren 1978) and theoretically may prevent the development of oropharyngeal thrush, budesonide was given via the tube spacer system. It was considered unlikely that the slightly altered deposition of drug particles in the lung produced by the tube spacer (Newman et al. 1980) would have any clinical effect in this study, since no therapeutic advantage over the conventional inhaler has been demonstrated with the bronchodilator drug terbutaline (Bloomfield et al. 1979; Gomm et al. 1980) unless the patients studied were incapable of using a pressurized aerosol efficiently (Godden & Crompton 1981). There is evidence, however, that some patients capable of using pressurized aerosols efficiently benefit from longer-term inhalation of terbutaline via the tube spacer (Spicer et al. 1980).

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Patients and Methods

Thirty out-patients (18 men, 12 women) with chronic bronchial asthma were included in the study. Their ages ranged from 18 to 67 years (mean 45.3 years). All patients were being treated with inhaled beclomethasone dipropionate, 400 μg daily, and had required within the preceding 12 months at least two courses of oral corticosteroid therapy for exacerbations of chronic asthma. Patients were not included in the study until at least four weeks had elapsed since treatment with prednisolone. Patients receiving daily systemic corticosteroid therapy were excluded from the trial. All patients could use a pressurized aerosol efficiently.

Beclomethasone dipropionate was administered four times daily via a conventional pressurized areosol. Budesonide was administered twice daily through a similar pressurized aerosol with a 'spacer' extension mouthpiece.

The study was designed as a double-blind cross-over trial with the following treatment regimens:

1. Beclomethasone dipropionate 100 μg (2 puffs) four times daily via conventional inhaler plus placebo (4 puffs) twice daily via 'spacer' extension mouthpiece.
2. Budesonide 200 μg (4 puffs) twice daily via 'spacer' extension mouthpiece plus placebo conventional inhaler (2 puffs) four times daily.

Each treatment regimen was administered for four weeks, with no intermediate 'washout' period, the order of treatment being decided by random allocation.

Patients completed diary cards, assessing symptoms for day and night by marking a 50 mm line labelled 'no symptoms' at zero and 'severe symptoms' at 50 mm. By this means symptoms of breathlessness, wheeze and cough were scored in millimetres. Peak expiratory flow rate (PEFR) was measured with a mini-Wright peak flow meter and recorded each day at 08.00 and 20.00 hours. Patients also recorded the frequency and times of salbutamol inhaler usage. Oral bronchodilator drugs were not used during the study.

Clinical assessments were made every two weeks, when the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured. All medical events were recorded and patients were asked if they had experienced any side-effects.

On entry to the trial, at four weeks and at eight weeks, the following investigations were performed: chest radiograph, haemoglobin, total white cell count and differential count, blood urea, creatinine, bilirubin, alkaline phosphatase, aspartate transaminase (AST), lactic dehydrogenase and short tetracosactrin (Synacthen) test.

The results were analysed using Student's *t*-test for paired comparisons, taking treatment order into account. Lung function tests were compared for first two weeks of each treatment, second two weeks of each treatment and all four weeks of each treatment. For chemistry and haematology measurements each treatment period was compared with base-line recordings at the start of the trial.

If an exacerbation of asthma severe enough to merit treatment with systemic corticosteroids developed, the patient was withdrawn from that month's treatment. When the exacerbation occurred during the first month of the study the patient was re-entered into the second treatment period four weeks after systemic corticosteroid therapy had been stopped.

RESULTS

In the 60 active treatment periods there were eight exacerbations of asthma severe enough to warrant treatment with oral prednisolone. These eight treatment failures occurred in seven patients, five during treatment with budesonide and three during treatment with beclomethasone. The patient who relapsed on both treatments received only seven days' treatment with budensonide and 11 days' treatment with beclomethasone. Results from this patient were, therefore, excluded from the overall analysis.

Table I. Lung function tests (mean ±SD)

Measurement	*Budesonide period*	*Beclomethasone period*	*P value (Student's paired t-test)*
Morning PEFR (litres/min)			
Weeks 1 & 2/5 & 6	347 ± 133 ($n=29$)	336 ± 122 ($n=28$)	$P>0.1$
Weeks 3 & 4/7 & 8	337 ± 135 ($n=27$)	333 ± 123 ($n=27$)	$P>0.1$
Weeks 1–4/5–8	339 ± 131 ($n=25$)	339 ± 126 ($n=25$)	$P>0.1$
Evening PEFR (litres/min)			
Weeks 1 & 2/5 & 6	366 ± 145 ($n=29$)	360 ± 131 ($n=28$)	$P>0.1$
Weeks 3 & 4/7 & 8	353 ± 145 ($n=27$)	355 ± 132 ($n=27$)	$P>0.1$
Weeks 1–4/5–8	352 ± 144 ($n=25$)	360 ± 135 ($n=25$)	$P>0.1$
FEV$_1$ (litres)			
At week 2/6 (i.e. following 2 weeks treatment)	2.04 ± 0.75 ($n=29$)	1.98 ± 0.76 ($n=28$)	$P>0.1$
At week 4/8 (i.e. following 4 weeks treatment)	2.07 ± 0.76 ($n=26$)	2.01 ± 0.81 ($n=25$)	$P<0.05$
FVC (litres)			
At week 2/6 (i.e. following 2 weeks treatment)	3.24 ± 1.15 ($n=29$)	3.17 ± 1.03 ($n=28$)	$P>0.1$
At week 4/8 (i.e. following 4 weeks treatment)	3.24 ± 1.10 ($n=26$)	3.23 ± 0.99 ($n=25$)	$P>0.1$

Lung function tests (Table I)

No significant differences were found in morning or evening PEFR for the two treatment periods compared two weekly and over the whole month. FEV$_1$ measured following four weeks on each therapy was significantly higher after budesonide therapy ($P<0.05$) and FVC followed the same trend but was not significantly higher.

Symptom scores and inhaler usage (Table II)

No significant differences were found in morning or evening wheeze, cough, breathlessness or bronchodilator inhaler usage between the two treatment periods.

Table II. Symptom scores and inhaler usage (mean ±SD)

*Measurement**	*Budesonide period*	*Beclomethasone period*	*P value (Student's paired* t-*test)*
Wheeze (mm)			
Morning score	6.33±7.98 ($n=27$)	5.24±6.39 ($n=27$)	$P>0.1$
Evening score	5.99±8.06 ($n=27$)	4.46±4.94 ($n=27$)	$P>0.1$
Breathlessness (mm)			
Morning score	6.45±8.92 ($n=27$)	3.92±5.57 ($n=27$)	$P>0.1$
Evening score	6.52±9.07 ($n=27$)	3.99±4.63 ($n=27$)	$P>0.1$
Cough (mm)			
Morning score	4.26±6.31 ($n=27$)	3.58±6.19 ($n=27$)	$P>0.1$
Evening score	4.10±5.99 ($n=27$)	3.10±4.36 ($n=27$)	$P>0.1$
Inhaler usage (No. of puffs)			
Morning score	1.44±1.05 ($n=27$)	1.34±1.09 ($n=27$)	$P>0.1$
Evening score	1.84±1.22 ($n=27$)	1.66±1.29 ($n=27$)	$P>0.1$

* Morning score represents symptoms and inhaler usage during the previous night. Evening score represents symptoms and inhaler usage during that day.

Clinical chemistry (Table III)

Statistical analysis of plasma cortisol levels showed no effect of budesonide or beclomethasone on either basal levels or response to tetracosactrin. Thus, there was no evidence that adrenal suppression occurred during the study. Similarly there were no significant changes in blood urea, bilirubin, AST and alkaline phosphatase levels. However, serum creatinine and lactic dehydrogenase levels rose significantly during treatment with budesonide ($P<0.01$ and $P<0.05$ respectively) but in no patient was there an elevation above the normal range.

Haematology (Table IV)

Analysis of values at the end of each treatment period for haemoglobin, RBC, platelets and total WBC showed no significant changes from pre-trial values although there was marginal statistical evidence of a higher total WBC ($P<0.1$) following beclomethasone.

Differential WBC following budesonide treatment showed no significant changes in any cell type although there was a significant reduction in neutrophils following beclomethasone ($P<0.05$).

Table III. Clinical chemistry (mean ± SD)

Measurement	*Initial pre-trial*	*After 1 month budesonide*	*After 1 month beclomethasone*	*Initial vs budesonide: P value for paired data*	*Initial vs beclomethasone: P value for paired data*
Basal plasma cortisol (μmol/litre)	0.47 ± 0.23 (*n* = 27)	0.45 ± 0.14 (*n* = 27)	0.48 ± 0.22 (*n* = 26)	$P > 0.1$	$P > 0.1$
Synacthen response (μmol/litre)	0.36 ± 0.18 (*n* = 25)	0.34 ± 0.13 (*n* = 27)	0.36 ± 0.18 (*n* = 25)	$P > 0.1$	$P > 0.1$
Creatinine (mmol/litre)	0.078 ± 0.012 (*n* = 18)	0.087 ± 0.016 (*n* = 18)	0.081 ± 0.019 (*n* = 18)	$P < 0.01$	$P > 0.1$
Urea (mmol/litre)	5.15 ± 1.46 (*n* = 24)	5.08 ± 1.74 (*n* = 25)	5.00 ± 1.36 (*n* = 25)	$P > 0.1$	$P > 0.1$
Bilirubin (μmol/litre)	9.44 ± 3.59 (*n* = 25)	9.12 ± 3.56 (*n* = 25)	9.96 ± 3.90 (*n* = 24)	$P > 0.1$	$P > 0.1$
Lactic dehydrogenase (U/litre)	318.7 ± 52.7 (*n* = 24)	339.5 ± 65.14 (*n* = 24)	331.3 ± 64.6 (*n* = 24)	$P < 0.05$	$P > 0.1$
Aspartate transaminase (U/litre)	17.96 ± 4.81 (*n* = 25)	19.0 ± 6.05 (*n* = 25)	19.08 ± 6.34 (*n* = 24)	$P > 0.1$	$P > 0.1$
Alkaline phosphatase (U/litre)	49.68 ± 21.85 (*n* = 25)	52.88 ± 21.69 (*n* = 25)	53.17 ± 20.10 (*n* = 24)	$P > 0.1$	$P > 0.1$

Table IV. Haematology (mean ± SD)

Measurement	*Initial pre-trial*	*After 1 month budesonide*	*After 1 month beclomethasone*	*Initial vs budesonide: P value for paired data*	*Intial vs beclomethasone: P value for paired data*
Haemoglobin (g/dl)	14.86 ± 1.17 ($n=29$)	14.83 ± 1.31 ($n=26$)	14.95 ± 1.11 ($n=27$)	$P>0.1$	$P>0.1$
RBC ($\times 10^{12}$/litre)	4.90 ± 0.31 ($n=29$)	4.94 ± 0.33 ($n=26$)	4.91 ± 0.32 ($n=27$)	$P>0.1$	$P>0.1$
Platelets ($\times 10^{9}$/litre)	231.8 ± 65.2 ($n=27$)	244.2 ± 59.4 ($n=25$)	212.2 ± 48.2 ($n=26$)	$P>0.1$	$P>0.1$
Total WBC ($\times 10^{9}$/litre)	6.81 ± 1.18 ($n=29$)	6.97 ± 1.22 ($n=26$)	7.19 ± 1.16 ($n=27$)	$P>0.1$	$P>0.05<0.1$
Neutrophils (%)	62.29 ± 10.11 ($n=24$)	63.77 ± 11.61 ($n=22$)	57.5 ± 11.17 ($n=24$)	$P>0.1$	$P<0.05$
Lymphocytes (%)	28.04 ± 8.68 ($n=24$)	25.86 ± 9.53 ($n=22$)	30.92 ± 8.41 ($n=24$)	$P>0.1$	$P>0.1$
Monocytes (%)	5.38 ± 2.6 ($n=24$)	5.50 ± 3.10 ($n=22$)	6.00 ± 3.05 ($n=24$)	$P>0.1$	$P>0.1$
Eosinophils (%)	4.04 ± 3.2 ($n=24$)	4.41 ± 3.38 ($n=22$)	5.04 ± 4.48 ($n=24$)	$P>0.1$	$P>0.1$
Basophils (%)	0.21 ± 0.51 ($n=24$)	0.41 ± 0.73 ($n=22$)	0.50 ± 1.02 ($n=24$)	$P>0.1$	$P>0.1$

DISCUSSION

The results of this study in 30 patients with chronic asthma indicate that budesonide administered for one month in a twice daily dose of 200 μg via a pressurized inhaler with tube spacer extension is as effective in the control of symptoms as beclomethasone 100 μg four times daily via a conventional pressurized inhaler. It could be argued that since a double placebo period was not included in our study design there is no evidence that beclomethasone treatment was necessary in the patients selected and hence no conclusions about the efficacy of budesonide can be drawn. However, we think that the likelihood of inhaled corticosteroids not being necessary in the patients studied is small since the population from which they were chosen is the same as that used for a study of beclomethasone conventional inhaler versus beclomethasone dry powder (Carmichael et al. 1978). In that study 75% of patients developed an exacerbation of asthma and since our clinical criteria for using beclomethasone have not changed we did not believe that the inclusion of a double placebo period in the present study was either necessary or ethical. It is possible, however, that both budesonide and beclomethasone administered twice daily would be as effective as beclomethasone four times daily, but this cannot be assumed from the present results and we are not aware of any published data which indicate that beclomethasone is effective when given twice daily.

Oropharyngeal candidiasis was not observed during this investigation and studies of much longer duration will have to be performed to assess whether the decreased deposition of drug in the mouth and throat afforded by the tube spacer extension has any influence on the development of thrush. To answer this question the ideal long-term study should be in patients not previously treated with an inhaled corticosteroid preparation in order to avoid susceptible patients being selected out by prior treatment. Many clinicians, including ourselves, believe that patients inhaling 'low velocity' dry powder beclomethasone (via the Rotahaler) have fewer problems with oropharyngeal thrush than patients inhaling 'high velocity' pressurized aerosol beclomethasone. Indeed it is our practice, when a patient being treated with beclomethasone develops thrush, to change treatment to the dry powder after appropriate local antifungal therapy. However, we are not aware of published reports which support the clinical impression that impaction of drug on to the mucosa of the fauces and posterior pharynx predisposes to the development of oropharyngeal thrush.

The finding that a corticosteroid aerosol is effective when inhaled twice daily should improve drug compliance since, in our experience, many patients with chronic asthma forget to take their treatment during the day but usually remember morning and evening doses. A corticosteroid aerosol with tube spacer extension may also improve compliance since many patients are unable to use conventional pressurized aerosols properly (Saunders 1965) even after careful tuition (Paterson & Crompton 1976). These patients obtain a better therapeutic effect with the bronchodilator drug terbutaline when they use a pressurized aerosol with a tube spacer extension (Godden & Crompton 1981)

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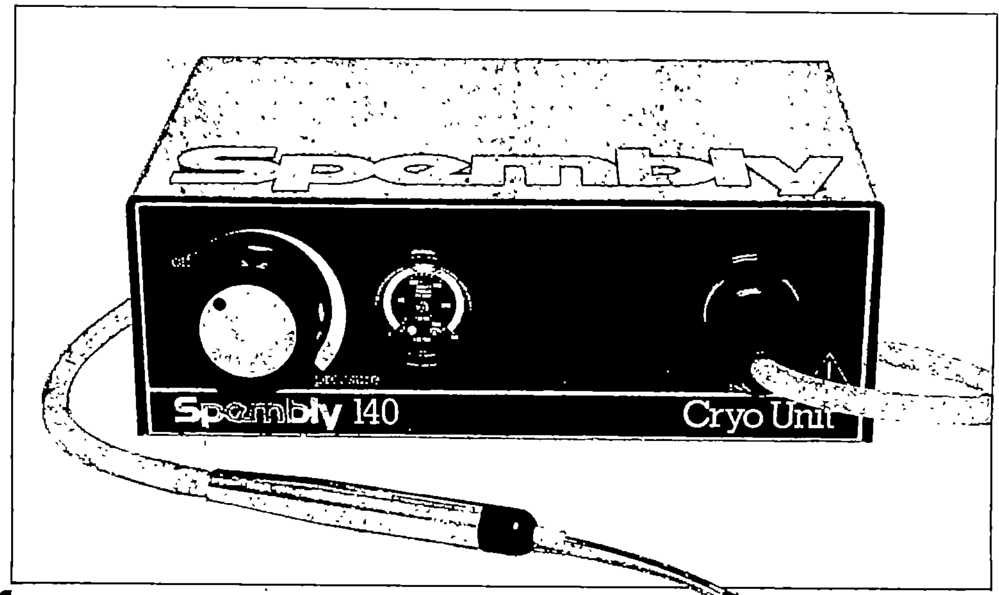

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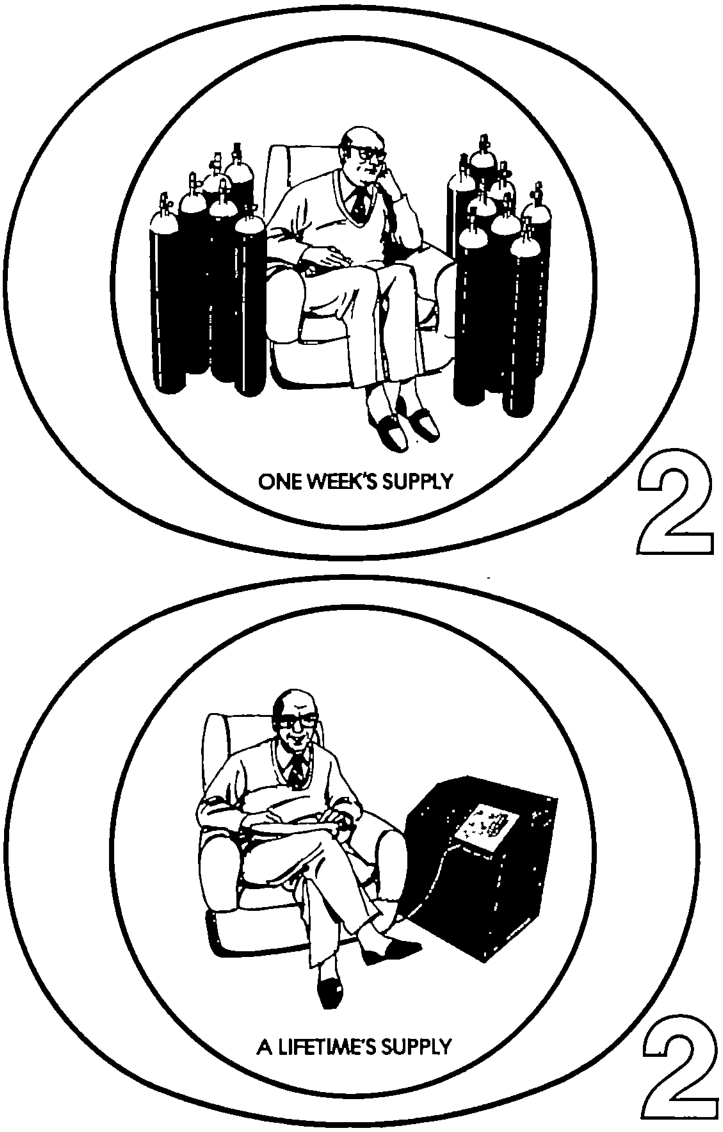

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Br. J. Dis. Chest (1982) *76*, 69

SEVERE ACUTE ASTHMA: A COMPARISON OF THREE METHODS OF INHALING SALBUTAMOL

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Summary

The effects of salbutamol inhaled by three different methods were compared in groups of adult patients with severe acute asthma. 2 × 400 μg Rotacaps was the optimum dose of dry powder but about 40% of patients failed to respond to it. 5 mg salbutamol nebulized with IPPB resulted in a significant increase in peak expiratory flow rate when given before or after either Rotacaps or salbutamol nebulized without IPPB, whereas neither the dry powder nor the nebulized drug without IPPB resulted in significant change when given after salbutamol nebulized with IPPB. The extra benefit derived with IPPB is only slight and requires a device of appropriate characteristics. Occasional patients fail to respond to salbutamol inhaled by any means, generally those with the most severe airflow limitation.

INTRODUCTION

Salbutamol is used widely in the management of severe acute asthma and can be given intravenously (Hetzel & Clark 1976; Williams & Seaton 1977; Johnson et al. 1978; Lawford et al. 1978; Bloomfield et al. 1979) or by inhalation as an aerosol, powder or nebulized solution (Webber et al. 1974; Leading Article 1978, 1981; Grimwood et al. 1981). The choice of method should be governed by efficacy, the incidence of side-effects and the resources required to provide the treatment. The availability of the very simple Rotahaler, and the continuing controversy about additional benefit if intermittent positive pressure breathing (IPPB) is used to deliver nebulized salbutamol (Choo-Kang et al. 1970; Choo-Kang & Grant 1975; Cayton et al. 1978; Campbell et al. 1978), prompted a comparison of these methods in patients with severe acute asthma requiring hospital admission.

Materials and Methods

Patients aged 16 years or more were recruited to the study only if the admitting medical officer was satisfied that treatment by inhaled salbutamol alone could be given without any other medication in the first instance. The diagnosis of asthma had been made previously in all cases on the basis of a measured variation of at least 20% in one or more index of expiratory airflow limitation in patients without evidence of other disease of the tracheobronchial tree. In particular, patients with variable airflow limitation complicating chronic bronchitis (Medical Research Council 1965) were not included. All patients agreed to participate in the trial after its implications had been explained to them.

Group 1

The optimum dose of the dry powder was defined in the first 20 patients who were studied before and after the inhalation of up to 4 × 400 μg salbutamol Rotacaps. All observations were made by a qualified physiotherapist who also supervised treatment. The heart rate was counted over 30 seconds. Two measurements of peak expiratory flow rate (PEFR) were made, separated by at least 30 seconds, and a third figure was recorded if the second was more than 10% higher than the first. The highest value was used for analysis. Measurements were made before the study began and five minutes after inhaling the contents of each of three or four capsules. Treatment stopped after three capsules if the PEFR failed to rise by at least 10% of the value recorded after the second.

Group 2

Another 21 patients were allocated at random to receive either 2 × 400 μg salbutamol Rotacaps followed 15 minutes later by 5 mg salbutamol nebulized during IPPB with a Bird Mark 7 ventilator, or the same treatment in reverse order. Salbutamol Rotacaps were the first treatment for 10 patients and salbutamol nebulized during IPPB was given first to the other 11.

All patients were treated either sitting upright or in the high side-lying position. Relaxation of the upper chest and shoulder girdle was encouraged. The settings of the ventilator allowed triggering with only minimal effort during IPPB and the pressure and flow controls were adjusted until the patient could sustain regular assisted ventilation without discomfort. Inspiration was terminated at a pressure between 1.1 and 1.5 kPa (11–15 cm H_2O) and the flow rate varied between the manufacturer's arbitrary settings of 7 and 12. All patients used a mouthpiece during IPPB but some required a nose-clip as well.

Group 3

The same selection criteria were used except that the admitting medical officer could, at his discretion, use a bolus or infusion of aminophylline before the study began. 24 patients in this group were allocated at random to receive nebulized salbutamol by one of two schedules. 12 received 5 mg salbutamol nebulized during IPPB as described above followed by a further 5 mg nebulized from a simple nebulizer (Inspiron Minineb) driven by 5 litres/min of oxygen, and 12 received these treatments in reverse order.

Heart rate and PEFR were recorded as previously. 15 patients received aminophylline, 10 having been given a bolus of 250 mg within an hour of the start of the study followed by an infusion of 80 mg/hour. The other five were receiving aminophylline by infusion but this had only just been established, no loading dose had been given and an effective blood level could not have been reached. Blood theophylline levels were not measured in any patient. Four of the 10 patients who were receiving what was judged to be a therapeutic dose of aminophylline, and three of the five in whom the infusion had just been begun, were treated with nebulized salbutamol with IPPB first; the other eight patients who had received aminophylline were given salbutamol nebulized from the simple inhaler first.

RESULTS

There were no significant differences between the groups before treatment (Table I).

Table I. Values for PEFR and heart rate before treatment (mean ± SD)

	PEFR (litres/min)	*Heart rate* (beats/min)
Group 1	105 ± 25	103 ± 15
Group 2	116 ± 44	105 ± 10
Group 3	118 ± 45	108 ± 20

Group 1

Values recorded from one patient were excluded because measurements of PEFR were not reproducible. Seven of the remaining 19 patients received three salbutamol Rotacaps and 12 received four. There was a progressive increase in mean PEFR after the first three capsules but although all patients either improved or did not change after the first two, five patients showed a slight fall in PEFR after the third capsule. There was no significant change in PEFR after the fourth capsule in the 12 patients who received this dose and changes in heart rate for all patients were insignificant throughout. Four patients failed to improve at all (increase in PEFR less than 10% of initial figure) and four more improved only slightly (increase in PEFR just 20% of an initial figure of 100 litres/min or less). The initial PEFR of these eight patients was lower than that of the 11 who responded well (89 and 116 litres/min respectively; $P < 0.02$) but the heart rates were similar (103 and 102/min).

Table II. Changes in PEFR and heart rate for patients in Group 2 (mean ± SD)

	PEFR (litres/min)		*Heart rate* (beats/min)
Before treatment	122 ± 35		106 ± 11
After 2 × 400 μg salbutamol Rotacaps	146 ± 44	$P < 0.01$	103 ± 12
After 5 mg salbutamol nebulized with IPPB	178 ± 49		111 ± 16
Before treatment	111 ± 52	$P < 0.002$	105 ± 11
After 5 mg salbutamol nebulized with IPPB	167 ± 88		104 ± 11
After 2 × 400 μg salbutamol Rotacaps	184 ± 102		104 ± 13

There were no significant differences except where shown.

Group 2.

The mean PEFR of patients given salbutamol Rotacaps before salbutamol nebulized during IPPB increased after both treatments but only the second increment reached statistical significance (paired *t*-test; Table II). Patients given nebulized salbutamol during IPPB before the Rotacaps also achieved a higher PEFR after each treatment, but only the increase after salbutamol nebulized during IPPB reached statistical significance. There were no significant changes in heart rate after either sequence.

The PEFR of eight patients failed to increase by 20% or more after their first treatment. Six had received salbutamol Rotacaps first and three subsequently showed a rise in PEFR of at least 20% after salbutamol during IPPB. Neither of the two patients who failed to respond to salbutamol nebulized during IPPB improved when subsequently given 2 × 400 μg salbutamol Rotacaps.

Group 3

The mean PEFR of patients given salbutamol with IPPB followed by nebulized salbutamol without IPPB increased progressively but only the first of the two increments in PEFR reached statistical significance (Table III). There was no change in heart rate. Patients treated in the reverse order showed a significant improvement in PEFR after both forms of treatment and the heart rate increased after the second but not the first dose of nebulized salbutamol. Six patients failed to improve with either form of treatment.

Table III. Changes in PEFR and heart rate for patients in Group 3 (mean ± SD)

	PEFR (litres/min)		*Heart rate* (beats/min)	
Before treatment	117 ± 43		105 ± 15	
After 5 mg salbutamol nebulized without IPPB	167 ± 64	$P<0.01$	102 ± 15	
After 5 mg salbutamol nebulized with IPPB	195 ± 86	$P<0.01$	113 ± 19	$P<0.001$
Before treatment	121 ± 48		111 ± 24	
After 5 mg salbutamol nebulized with IPPB	155 ± 62	$P<0.001$	107 ± 25	
After 5 mg salbutamol nebulized without IPPB	164 ± 75		105 ± 22	

There were no significant differences except where shown.

DISCUSSION

Although all patients had required hospital admission as an emergency, their inclusion in the trial depended on the judgement of the admitting medical officer to rely on inhaled treatment alone at first. Any patient whose condition gave rise to particular anxiety was excluded.

Vitually all patients reported that salbutamol as a pressurized aerosol was no longer effective but more than 50% showed an increase in PEFR of 20% or more after inhaling salbutamol as the dry powder. The response after three or four 400 μg salbutamol Rotacaps was more variable than after the first two capsules and so this was regarded as the optimum dose with which to compare the recommended dose (5 mg) of nebulized salbutamol (Spitzer et al. 1972). The administration of inhaled salbutamol as the dry powder cannot, however, be recommended for those with an exacerbation of asthma requiring hospital admission because patients who failed to respond or responded poorly were those with the lowest initial PEFR. In addition, there were three patients in group 2 who failed to respond to salbutamol Rotacaps but who then improved when given nebulized salbutamol during IPPB. This could be a dose related effect but such an explanation appears unlikely because no patient who failed to respond to salbutamol nebulized during IPPB improved subsequently when given the dry powder.

The superiority of delivering nebulized salbutamol during IPPB has been reported in several studies (Choo-Kang et al. 1970; Choo-Kang & Grant 1975; Cayton et al. 1978) but could not be demonstrated in patients recovering from an acute attack (Webber et al. 1974). A comparison (Campbell et al. 1978) of nebulized salbutamol delivered with or without IPPB to patients acutely ill with asthma failed to show any benefit with positive pressure, but did demonstrate a greater increase in heart rate. In the present series, nebulized salbutamol with IPPB resulted in a significant improvement whether it was given before or after salbutamol inhaled by a different technique. Thus, our findings favour the use of IPPB, although the benefit must be regarded as marginal. The concomitant administration of aminophylline to some of these patients has to be considered too but it seems unlikely that this influenced the outcome because it was given to approximately equal numbers of patients following the two salbutamol treatment schedules.

Changes in heart rate were trivial throughout and did not show an increase when salbutamol with IPPB was given as the first form of treatment. The discrepancy between these results and the study by Campbell et al. (1978) may be explained perhaps by the choice of ventilator and its method of use. Ayres et al. (1963) have shown that the work of breathing during IPPB approaches zero in relaxed subjects. An anxious or poorly relaxed subject may do more work with IPPB than when breathing without it and this work would increase even more in those with airflow limitation if a device with a fast inspiratory flow rate is used because dynamic pulmonary compliance in such patients is inversely proportional to inspiratory flow rate. Any increase in the work of breathing during IPPB is likely to cause or exacerbate tachycardia. Relief from the work of breathing would be an asset in the management of patients distressed and tired by dyspnoea, particularly in the most severely ill, but a ventilator with a variable inspiratory flow rate and an experienced therapist are required to help anxious patients relax. Both are expensive resources and the additional benefit achieved when nebulized salbutamol with IPPB is delivered expertly is not so great that its widespread use can be regarded as mandatory. The possibility of creating or enlarging a pneumothorax with IPPB must also be considered (Karetzky 1975), although the risks are small if low inflation pressures and a slow inspiratory flow rate are used.

We conclude that the delivery of nebulized salbutamol with IPPB for the treatment of severe acute asthma does have advantages over the inhalation of either the dry powder or the nebulized solution without IPPB. Experienced personnel and an appropriate mechanical ventilator are required if the best results are to be achieved and comparable benefit can be obtained for the majority of patients by salbutamol nebulized in a simple gas-driven device.

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Br. J. Dis. Chest (1982) *76*, 75

REPRODUCIBILITY OF THE TINE TUBERCULIN TEST*

RESEARCH COMMITTEE OF THE BRITISH THORACIC ASSOCIATION

Summary

The reproducibility of the Tine tuberculin test was assessed by paired tests on 180 subjects. Using the recommended method of measurement, there was lack of agreement in 23%. The discrepancies were reduced to 18% using a different method. There were no examples of a subject with a negative response on one arm and a positive response on the other. The discrepant results always involved reactions classified as doubtful or intermediate on one arm with a stronger or weaker reaction on the other. Thus there remains doubt about the ability of the Tine test to produce consistent reactions in tuberculin-positive subjects.

INTRODUCTION

In an earlier study comparing the Tine tuberculin test with the Mantoux test the Research Committee of The British Thoracic Association (BTA) found that agreement between the two tests was sometimes lacking (Lunn & Johnson 1978). The Tine test has the advantage of being simple to apply, sterile and disposable, but in the past there have been conflicting reports on its reliability (Furcolow et al. 1968; Bowder & Griffin 1972; Welke et al. 1976; Sinclair & Johnston 1979). Before attempting to identify reasons for this, the Research Committee decided to determine whether the test was reproducible in clinical practice. Without this the test cannot be accepted as a reliable indicator of tuberculin sensitivity. While this work was in progress the results of another study have suggested that discrepancies in the detection of tuberculin sensitivity may occur with the Tine test because of lack of uniformity of tuberculin coating of the tines (Lunn 1980). The study reported here sought to ascertain whether, in clinical practice, it was possible to perform reproducible Tine tests using the currently available Tine test units.

Methods

Five centres agreed to provide subjects in the age range 18–80 years who were likely to be tuberculin positive and not suffering from active tuberculosis. Subjects receiving systemic corticosteroids, or who had been recently immunized or who were pregnant were excluded. Tine tuberculin tests (Lederle Limited) from a single batch (No. 542–565, expiry date 21 June 1980) were obtained commercially. Two Tine tests were performed on each subject, one on each forearm, according to the method recommended by the manufacturers.

Two methods of reading were used for each site. Method 1 followed the recommended method (National Tuberculosis and Respiratory Diseases Association 1969) in recording the greatest diameter of induration at each puncture site or of coalesced sites, the reactions being classified negative (0–1 mm), doubtful (2–4 mm) and positive (≥5 mm). When measurements fell between two numbers on the scale, the lower value was recorded.

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* This study was organized by a subcommittee of the Research Committee of The British Thoracic Association whose members were: Dr A. J. Johnson (*Chairman*); Mr G. Berry, Dr J. A. Lunn, Dr A. R. Somner and Dr V. H. Springett.

Method 2 recorded the visible reactions whether or not induration was present, with O = no visible or palpable response, V = number of responses visible but not palpable, P = number of discrete papules palpable, C = coalescence of two or more papules, R = raised uniform disc without central depression and U = ulceration. Grades O and V were regarded as negative reactions, P as intermediate or doubtful and grades C, R and U as positive reactions.

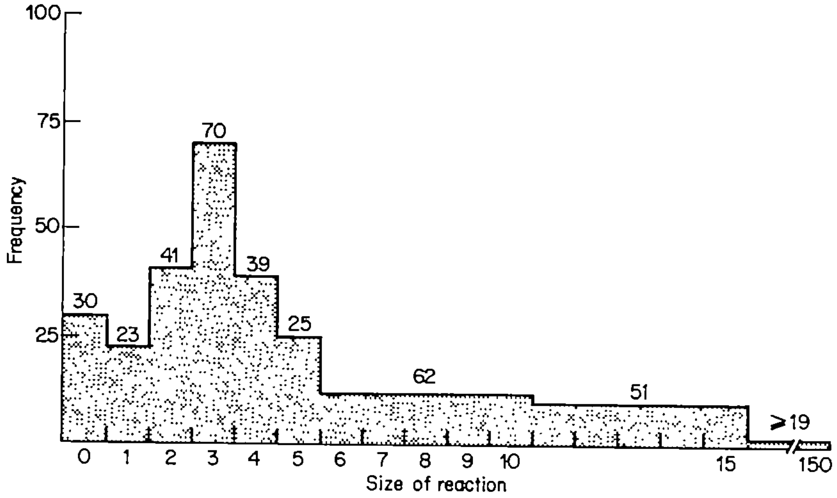

Fig. 1. Distribution of 360 Tine tests by Method 1

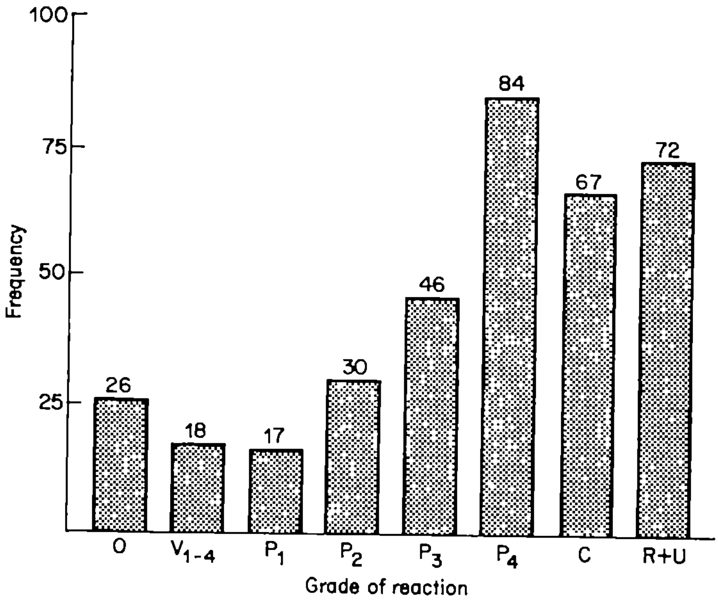

Fig. 2. Distribution of 360 Tine tests by Method 2

RESULTS

Paired tests in 180 subjects were analysed. 91 (51%) subjects gave a history of BCG vaccination and in 70 a scar was observed. The distribution of reactions by both reading methods is recorded in Figs 1 and 2 and shows a wide range of reactions.

Table I. Comparison of maximum Tine diameter on each arm by Method 1

Right arm	*Left arm*			
	0–1 mm	2–4 mm	⩾5 mm	Total
0–1 mm	20	6	0	26
2–4 mm	7	54	14	75
⩾5 mm	0	15	64	79
Total	27	75	78	180

Negative = 0–1 mm; doubtful = 2–4 mm; positive = ⩾ 5 mm.

Table I gives the results of the tests using Method 1. No subject had a positive reaction on one arm and a negative reaction on the other. In 23% of subjects there was a doubtful reaction on one arm with a positive or negative response on the other. (Of the 75 doubtful reactions on the left arm, six gave a negative reaction on the right arm and 15 a positive reaction: among the 75 doubtful reactions on the right arm, seven were negative and 14 were recorded as positive on the other arm, i.e. 42 discrepant results out of 180 = 23%.) The doubtful category accounted for 42% (75 on each arm) of all reactions.

Table II. Comparison of Tine test reactions on each arm using Method 2

Right arm	*Left arm*			
	O+V	P	C+R+U	Total
O+V	18	4	0	22
P	4	72	12	88
C+R+U	0	13	57	70
Total	22	89	69	180

O+V = negative; P = intermediate or doubtful; C+R+U = positive.

Table II shows the results recorded by Method 2 and these have been grouped to give patterns which correspond approximately to those recorded by Method 1. Again, there were no subjects with a positive reaction on one arm and a negative on the other. However, 18% of subjects showed an intermediate or doubtful reaction on one arm with either a positive or negative response on the other. (Of the 89 intermediate reactions on the left arm, the reaction was negative in four on the other arm and positive in 13, while of the 88 intermediate reactions on the right arm, the reaction was negative in four on the left arm and positive in 12, i.e. 33 discrepant readings out of 180 = 18%.) Using this classification 49% of the responses fell in the intermediate or doubtful group. The incidence of discrepancies between paired tests was similar in each centre.

DISCUSSION

The subjects included in this study had received BCG or were thought to be tuberculin-positive. Therefore there were relatively few negative responses. A clean-cut difference between tests which showed no reaction and those in which a reaction of any size occurred was not obtained with either method of reading. Measurement differences as small as 1 mm by Method 1 are difficult to estimate and so some reactions might be arbitrarily recorded either as positive or doubtful or else as negative or doubtful. Thus, the narrow scale of measurement may have contributed to the significant discrepancy rate between the paired tests. For these reasons, reading of the test by Method 1 presents difficulties in clinical use. Method 2 is probably an easier reading method but even so there are discrepancies with this method, though they are fewer than with method 1. The point at which the size of the reaction should be regarded as positive has not been determined for Method 2.

The Tine test has the advantage of ease and speed of use, together with disposability. It is to be hoped that the reproducibility of the test can be improved by improving the uniformity of tuberculin coating of the tines. There is still a need to decide upon the best method of reading.

ACKNOWLEDGEMENTS

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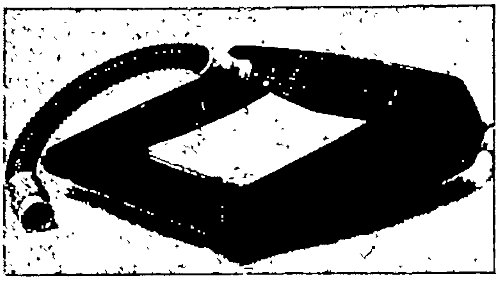

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ALCOHOL IN ASTHMA AND THE BRONCHOCONSTRICTOR EFFECT OF CHLORPROPAMIDE

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Summary

The effect of drinking 40 ml of sherry on peak expiratory flow rate in 16 normal subjects and 19 patients with asthma was assessed after oral administration of either chlorpropamide or placebo. After placebo and sherry normal subjects showed no change in peak expiratory flow rate, while an increase was usually shown by patients with asthma. This bronchodilatation was more marked in patients whose base-line peak flow rate was less than 50% predicted. Ingestion of chlorpropamide before sherry significantly modified the bronchodilating properties of sherry; five of the 19 patients with asthma showed airway narrowing on 11 of 19 occasions tested. Further studies in one patient suggest that this bronchoconstriction may be mediated by congeners in sherry rather than ethanol. These findings confirm the observation that chlorpropamide and sherry can cause airway narrowing in patients with asthma but shows that this response is not always reproducible. The bronchodilator effect of alcohol in patients with asthma may have therapeutic implications.

INTRODUCTION

It has been known for many years that some patients with diabetes mellitus who take chlorpropamide show an intolerance for alcohol (Fitzgerald et al. 1962). After drinking alcohol these patients complain of intense facial flushing (the chlorpropamide–alcohol flush, CPAF) sometimes associated with mild nausea, headache, abdominal discomfort and, in a few cases, breathlessness. Leslie and Pyke (1978) have suggested that this phenomenon is a genetic marker of a large sub-set of patients with non-insulin-dependent diabetes who are relatively less susceptible to the large and small vessel complications of diabetes (Barnett & Pyke 1980; Leslie et al. 1979). They also showed that a proportion of their patients taking chlorpropamide became breathless following challenge with sherry and that the dyspnoea was associated with airway narrowing if asthma coexisted (Leslie et al. 1980).

This study reports the airway response to sherry with and without chlorpropamide in normal volunteers and in patients with asthma.

Subjects and Methods

Two groups of subjects were studied: 16 normal volunteers (10 female and six male, mean age 24.6 years) who gave no history of allergic reactions, hayfever, eczema or wheeze, and 19 patients with a clinical history of asthma (11 female and eight male, mean age 33.5 years). All patients with asthma had positive skin tests. Five were taking no regular therapy but the remainder required regular inhaled bronchodilators to control their asthma; two patients were also taking oral steroid therapy. No subject had diabetes mellitus.

In each study the subject took either 250 mg of chlorpropamide or a placebo tablet (the order being randomized in a single blind manner) 24 hours before the study. After an overnight fast a second tablet was taken two hours before the time of study. Using a Wright's peak flow meter, base-line values of peak expiratory flow rate (PEFR) were taken until six approximately constant values were obtained. The average of these six readings was taken as the mean base-line value for that study. Every study was started at the same time in the morning and each mean base-line value was within 10% of all other studies for that subject.

The subject then drank 40 ml of a stock sherry in one minute and two PEFR readings were taken every 2½ minutes for 30 minutes and every five minutes for a further 30 minutes. The mean of each pair of readings was used in subsequent analysis. Further studies were performed on the patient with asthma to assess the reproducibility of the airway response. For these later studies, the frequency of measurements was reduced to every five minutes for one hour.

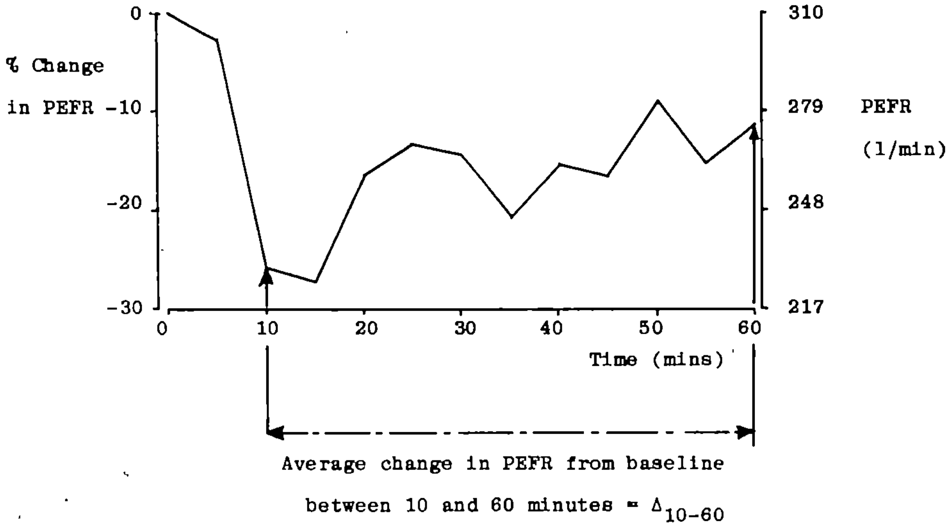

Fig. 1. An example of the airway response to sherry following chlorpropamide, showing the calculation of Δ_{10-60}.

When airway narrowing occurred, the fall in PEFR followed the pattern shown in Fig. 1. In the past, the area under the curve has been used for analysis of the time course but we have used the mean change in PEFR from base-line between 10 and 60 minutes – Δ10–60. This is derived as follows. PEFR is measured at time i, where i = 10 to 60 min.

$$\Delta_{10-60} = \sum_{i=10}^{=60}(\text{PEFR}_i - \text{PEFR}_{\text{base-line}}) \times \frac{1}{11}$$

From this it can be calculated that the area under the curve (A) is proportional to Δ_{10-60} as follows

$$\Delta_{10-60} = \frac{A}{\text{Total time}}$$

(where total time = 50 minutes)

Therefore Δ_{10-60} has been used as it gives a real numerical value (rather than a derived value) to the change in PEFR from base-line over the period of each study or group of studies. We have presented the data both in terms of absolute values (Δ_{10-60}) and in terms of percentage change ($\%\Delta_{10-60}$) for direct comparison of the two approaches but the results are exactly the same using either method. Throughout the results and discussions sections we have therefore used $\%\Delta_{10-60}$ as this is easier to visualize when comparing sets of data.

RESULTS

The results are summarized in Table I.

Normal volunteers

There were no significant changes in PEFR in normal volunteers with sherry following placebo and there was no significant difference between the values of $\%\triangle_{10-60}$ for the placebo studies compared to the chlorpropamide studies.

Patients with asthma

The first analysis compared the effects of placebo and chlorpropamide on the response to sherry in the initial pair of challenges in all 19 patients. With sherry following placebo, the average value for $\%\triangle_{10-60} = +5.8\%$. When sherry followed chlorpropamide, the average value for $\%\triangle_{10-60}$ was $+0.2\%$; this response was significantly lower than that produced by placebo plus sherry ($P < 0.025$).

Additional studies were performed on 14 of these 19 patients, making a total of 45 studies with sherry following placebo and 54 studies with sherry following chlorpropamide. For each patient, mean values of $\%\triangle_{10-60}$ were calculated for both chlorpropamide and placebo studies. Paired *t*-tests comparing the responses in placebo studies with those following chlorpropamide also showed a significant difference ($P < 0.025$) with a greater mean rise in PEFR following placebo. A fall in PEFR occurred in five patients on 11 occasions of 19 studies of sherry plus chlorpropamide. Thus, in these five patients, airway narrowing occurred in 57.9% of challenges. One patient showed airway narrowing on all five occasions tested, one on three of four occasions tested and the remaining three patients on one occasion out of one, three and four occasions respectively.

Overall, the changes in PEFR for patients with asthma following challenges after placebo or chlorpropamide are seen in Fig. 2. With sherry following placebo there is a slight but significant rise in PEFR from base-line, whereas following chlorpropamide, sherry results in a net fall in PEFR which only returns towards base-line by 60 minutes.

Influence of base-line values

The values of $\triangle_{10-60}$ and $\%\triangle_{10-60}$ have been plotted against their respective base-lines, expressed as a percentage of the predicted value (Figs 3, 4). With sherry challenge following placebo, bronchodilatation was produced in patients with lower % predicted PEFR values (Figs 3A, 4A). Of the 14 studies which started at a PEFR of less than 50% predicted, 10 (71%) showed a value of $\%\triangle_{10-60}$ of greater than +10% and five (36%) a value of greater than +20%.

Of the 11 studies where sherry challenge following chlorpropamide produced airway narrowing, 10 (91%) started from a base-line which was below 80% predicted (Figs 3B, 4B).

Table I. Summary of results

	No. of studies	*Mean base-line PEFR* (litres/min) (Mean ± SD)	Δ_{10-60} (litres/min) (Mean and range)	$\%\Delta_{10-60}$ (Mean and range)	*Paired t-test*	
					Δ_{10-60}	$\%\Delta_{10-60}$
Normal subjects						
Placebo	16	472 ± 88.7	+7.2 (− 8.3 to +21.8)	+1.2 (− 2.5 to + 4.3)	$t=0.72$	$t=0.21$
Chlorpropamide	16	472 ± 75.9	+3.9 (−18.9 to +36.4)	+1.0 (− 3.0 to + 9.0)	NS	NS
Asthmatics (first pair of readings)						
Placebo	19	339 ± 134.4	+12.9 (−18.5 to +61.3)	+5.8 (− 3.9 to +28.4)	$t=2.79$	$t=2.69$
Chlorpropamide	19	342 ± 138.8	−4.6 (−66.9 to +63.6)	+0.2 (−19.3 to +22.2)	$P<0.025$	$P<0.025$
Asthmatics (Multiple studies)						
Placebo	45	346 ± 142.6	+15.0 (−24.6 to +74.3)	+6.6 (− 7.3 to +37.7)	$t=3.29$	$t=2.59$
Chlorpropamide	54	357 ± 140.2	−0.5 (−82.6 to +63.6)	+1.4 (−27.0 to +22.9)	$P<0.005$	$P<0.025$

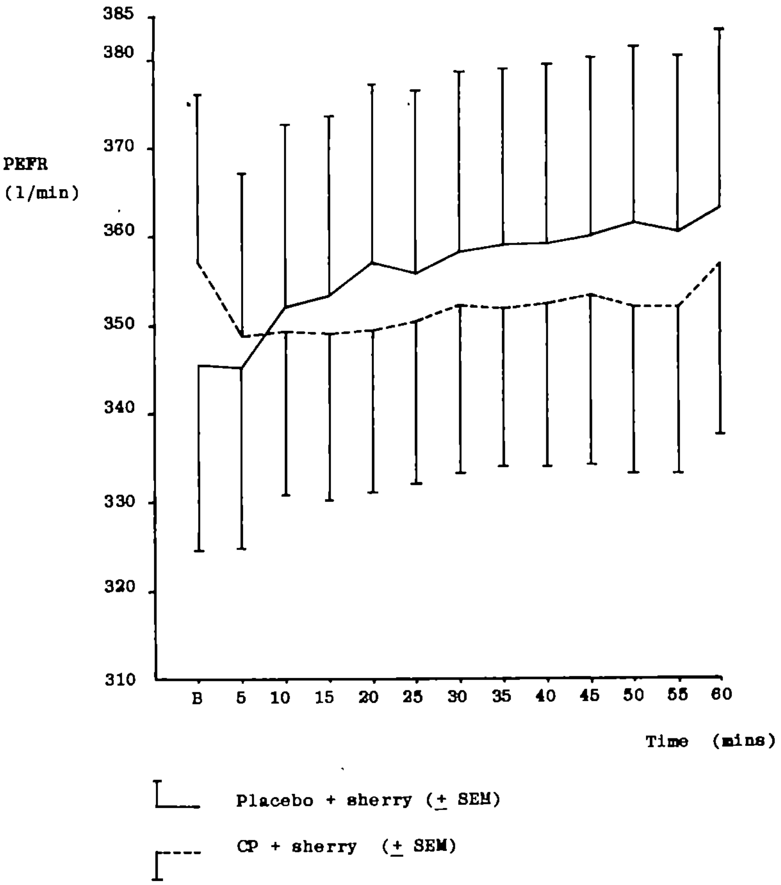

Fig. 2. Mean values of PEFR with sherry following placebo ($n=45$) or chlorpropamide ($n=54$) in 19 patients with asthma

Blockade studies

One patient showed a reproducible response to sherry following chlorpropamide on five of five occasions tested (average $\%\Delta_{10-60}=-19.3\%$; range $=-11.2\%$ to -27.7%). She was therefore chosen for further studies; she was given 40 ml of 40% ethanol (instead of sherry) following chlorpropamide; this resulted in an increased value of $\%\Delta_{10-60}$ of $+16.8\%$. On another occasion, tolbutamide was substituted for chlorpropamide when $\%\Delta_{10-60}$ was -9.5%. To assess the possible role of enkephalins in the response, she was studied again with sherry following chlorpropamide. On the first occasion, 2 mg of naloxone was given by slow intravenous injection, beginning five minutes before sherry and continuing for five minutes after the drink. On the second occasion, normal saline was substituted for naloxone. On both occasions, the response was similar to her previous challenges with sherry following chlorpropamide ($\%\Delta_{10-60}=-35.8\%$ and -21.9% respectively).

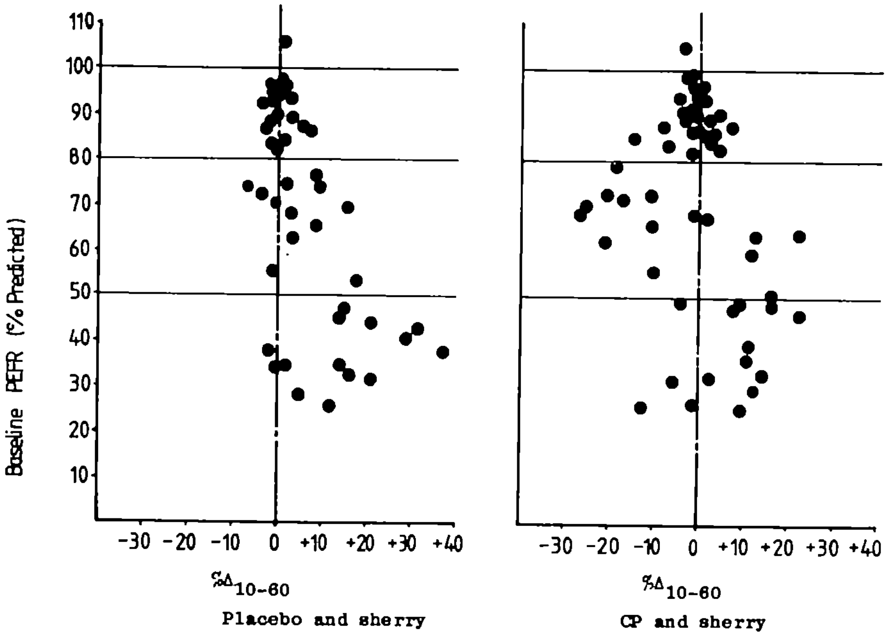

Fig. 3. Percentage change in PEFR after sherry challenge in 19 patients with asthma following either placebo ($n = 45$) or chlorpropamide ($n = 54$)

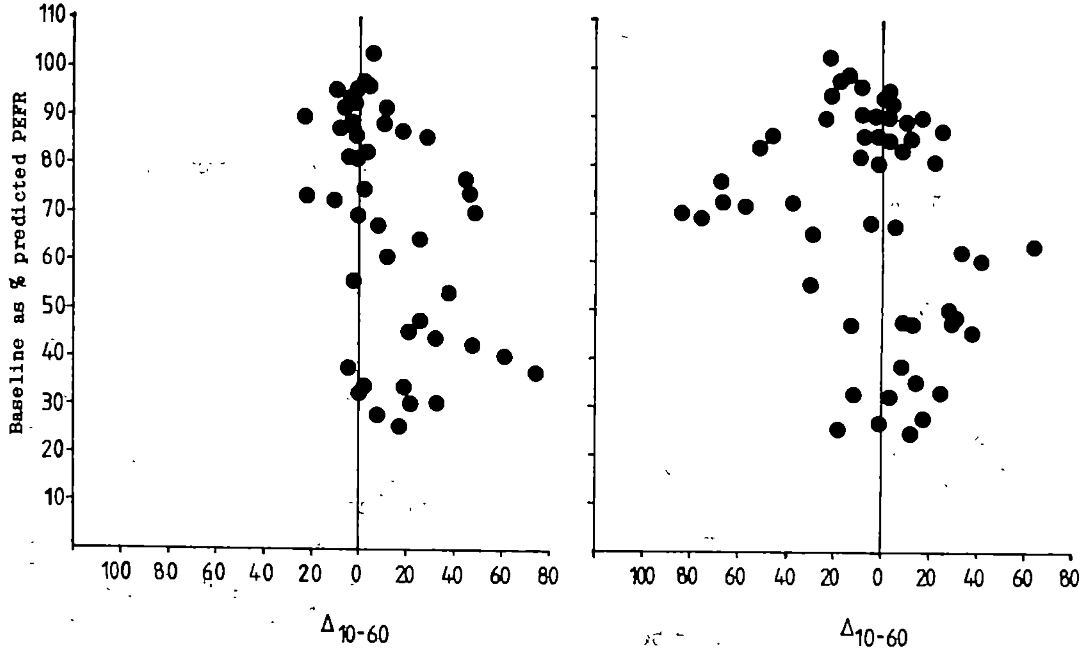

Fig. 4. Absolute changes in PEFR (litres/min) in nine patients with asthma following either (left) placebo ($n = 45$) or (right) chlorpropamide ($n = 54$)

Discussion

It has been known for many years that a proportion of patients taking chlorpropamide are unable to tolerate alcohol (Fitzgerald et al. 1962). A recent study by Leslie et al. (1980) showed that dyspnoea accompanying this reaction was associated with the development of airways obstruction as assessed by a fall in FEV_1' after challenge with sherry. Our results provide further information about this observation. Healthy subjects were unaffected by this combination but patients with asthma showed a variable response; chlorpropamide with sherry sometimes, but not always, caused airway narrowing.

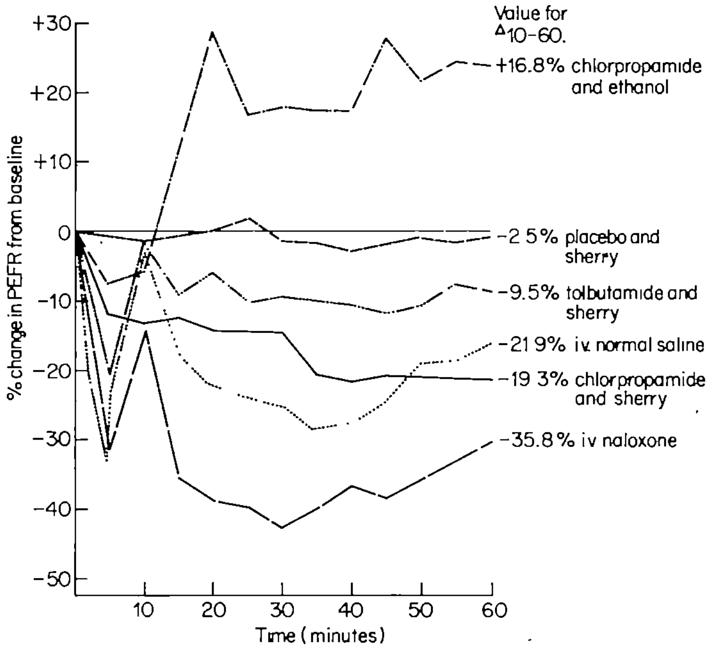

Fig. 5. Airway response to chlorpropamide and sherry, placebo and sherry, tolbutamide and sherry and chlorpropamide and ethanol and the effect of intravenous naloxone and intravenous normal saline on the airway responses to chlorpropamide and sherry in one patient who consistently wheezed with chlorpropamide and sherry

Studies with sherry following placebo (i.e. sherry alone) produced either no change in PEFR or bronchodilatation; those patients who showed a bronchodilator response usually had initial base-lines less than 50% predicted. However, when chlorpropamide was taken before the sherry, this pattern of response was modified. The combination of chlorpropamide with sherry produced three types of response which can be classified according to base-line PEFR values (see Figs 3B, 4B):

1. Those with an initial PEFR of greater than 80% predicted usually showed no response.
2. Those with initial PEFR values between 50 and 80% predicted showed airway narrowing in 57% of studies.
3. Those with initial base-line PEFR values of less than 50% predicted showed bronchodilatation but to a less marked degree than with sherry alone.

Although the study set out to examine the combination of sherry and chlorpropamide, our results suggest that some patients with asthma may develop bronchodilatation following intake of alcohol. This response was best seen in those patients with a reduced baseline PEFR; those with little or no reduction in base-line PEFR who showed no airway response might, however, have a bronchodilator response on days when their PEFR is at a lower level. Although a placebo response cannot be ruled out this apparently beneficial effect of alcohol in asthma has been described before, first by Salter in 1863 and latterly by Herxheimer and Stresemann (1963) and by Davis et al. (1980).

When chlorpropamide was taken before the sherry challenge, airway narrowing was seen in 11 of 54 studies on 19 patients with asthma, these 11 responses being confined to five patients. For these five patients, the reproducibility of the response was therefore 57.9%. This confirms that airway narrowing in response to chlorpropamide and sherry can occur in asthma but shows that the response is not found in all asthmatic patients and is only poorly reproducible when repeatedly tested in susceptible asthmatic patients. This poor reproducibility may be explained by the findings that patients with non-insulin-dependent diabetes taking long-term chlorpropamide are more likely to be CPAF-positive and to have higher chlorpropamide blood levels, than those whose diabetes is controlled with other oral hypoglycaemic agents (Jerntorp et al. 1981). It is therefore possible that if chlorpropamide was taken for a longer period prior to challenge with sherry the incidence and reproducibility of airway response might increase in patients with asthma.

Breslin et al. (1973) have described patients in whom attacks of asthma can be induced by specific alcoholic drinks. In our patients, sherry was not the cause of airway narrowing as no subject wheezed with sherry after placebo. Breslin et al. also found that asthmatic attacks were caused by congeners in the drinks rather than the ethanol itself. Our one patient who consistently showed airway narrowing with sherry following chlorpropamide developed a value for $\%\Delta_{10-60}$ of +16.8% with ethanol following chlorpropamide, suggesting that the bronchoconstriction that follows sherry and chlorpropamide is also related to some substance in the sherry other than ethanol. Our findings also suggest that in some cases, chlorpropamide might sensitize the bronchi of patients with asthma to bronchial irritants. Diabetic patients receiving chlorpropamide and who also have asthma should therefore be warned of the possible deleterious effects that alcohol may have on their asthma.

Leslie et al. (1980) also raised the possibility that asthma associated with alcohol and chlorpropamide is mediated by peptides with opioid activity such as enkephalins. Two of their patients had the synthetic enkephalin DAMME infused intravenously to test this hypothesis and one showed a fall in FEV_1. Butland et al. (1980) found no effect of DAMME infusion on FEV_1 or FVC in six normal subjects and suggested that the fall in FEV_1 found by Leslie et al. in one patient may have been caused by hyperventilation induced by enkephalin, a reaction noticed by Butland et al. in one of their subjects. The one patient in our study who was studied with naloxone showed no modulation of the airway narrowing induced by sherry following chlorpropamide. Despite the lack of reproducibility of the response in our group of patients with asthma, this finding does not support the idea that the mechanism of the response is mediated via opioid peptides.

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SELECTIVE BRONCHOGRAPHY USING THE FIBREOPTIC BRONCHOSCOPE

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Suspected bronchiectasis is still the most common indication for bronchography. Full bilateral bronchography is, however, an unpleasant procedure for the patient and can be dangerous or even fatal (American College of Chest Physicians 1967), particularly in patients with diminished respiratory reserve (Christafordis et al. 1962; Ansell 1976). Fibreoptic broncoscopy, in comparison, is widely used, safe and well tolerated by patients (Johnson et al. 1978).

It is often possible to make a diagnosis of bronchiectasis with clinical features and plain chest radiograph. If some form of contrast study is necessary, a selective bronchogram may suffice.

Many techniques for selective segmental catheterization and bronchography have been described, the catheters being guided into the segments of interest under fluoroscopic control; this is not, however, always technically possible.

Fibreoptic bronchoscopy allows direct visualization of segments of interest and the possibility of direct placement of catheters. Previous techniques described involve the placement of guide wires, removal of the bronchoscope and subsequent threading of a catheter over the guide wire (Fennessy 1970; Lutch & Ryan 1979). This is repeated for each segment.

We describe a technique using fibreoptic bronchoscopy for direct placement of a catheter for selective bronchography which allows sequential study of segments without removal of the bronchoscope.

Methods

After premedication patients were placed on a screening couch with a 'C' arm fluoroscope unit. Full fibreoptic bronchography was carried out under local anaesthetic in the normal way (Johnson et al. 1978; Clarke & Knight 1977). Any bronchial secretion or pus was aspirated and submitted for bacteriological and cytological study.

Following clearing of the segment of interest, a size 7 angiocatheter, 100 cm long, was passed down the centre channel of the bronchoscope and manipulated under direct vision and fluoroscopic check into the segment and the bronchoscope was withdrawn to the carina. A 3–5 ml bolus of Dionosil oily, previously warmed to reduce viscosity, was the injected down the catheter from a 5 ml plastic syringe by manual pressure.

The segmental bronchogram produced could then be studied in any plane using the 'C' arm fluoroscopic unit, improved if necessary by repositioning the patient on the couch; representative permanent films were then taken. If more than one segment was to be studied, the catheter tip was drawn back to the bronchoscope and the new segment catheterized as before, making removal of the catheter or the bronchoscope from the patient unnecessary.

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RESULTS

We have used this technique in 12 patients to date. It is our experience that it is easy to catheterize any desired segment providing the orifice is patent. An example of the quality of bronchograms obtained is illustrated in Fig. 1.

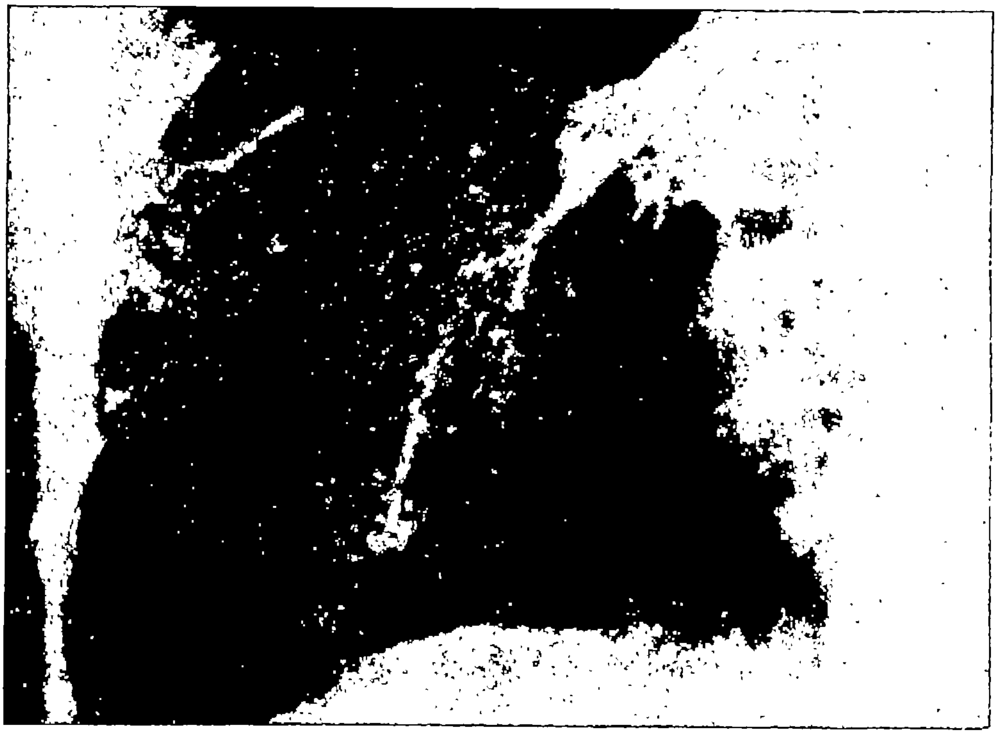

Fig. 1. Normal middle lobe bronchogram in patient referred because of recurrent middle lobe pneumonia

DISCUSSION

Indications for selective bronchography include:

1. Confirmation of localized bronchiectasis suggested by recurrent symptoms at one site which either is normal on plain radiograph or shows changes too slight or not sufficiently diagnostic for bronchiectasis.
2. Cases of unexplained haemoptysis where on bronchoscopy the segment from which the haemorrhage arises is identified by fresh bleeding but no mucosal abnormality is visible.
3. Patients with diminished respiratory reserve in whom a routine bronchogram would be contraindicated.

The advantages of using the fibreoptic bronchoscope in the performance of bronchograms are manifold. Full bronchography using conventional methods is unpleasant for the patient; considerable hypoxia may occur particularly in patients with diminished respiratory reserve (Christafordis et al. 1962). Fibreoptic bronchoscopy in comparison is safe and well tolerated (Johnson et al. 1978). Considerably less hypoxia occurs; the mean fall in arterial Po_2 is less than 9 mmHg and even this can be avoided by premedication with atropine (Neuhause et al. 1978). Before selective instillation of the contrast medium, the target bronchus can be examined, thus increasing the diagnostic yield, and all secretions can be cleared, improving the quality of the bronchograms obtained and providing uncontaminated specimens for bacteriology. Furthermore, the local anaesthetic prevents coughing with attendant 'alveolarization' of contrast, which may obscure the bronchial outline.

The techniques using guide wires (Fennessy 1970; Lutch & Ryan 1979) are difficult and displacement of the guide wire may occur during removal of the bronchoscope. For more than one segment to be studied, the whole procedure has to be repeated, which is time-consuming and uncomfortable for the patient.

The direct instillation of contrast medium down the suction channel of the bronchoscope is described (Oho & Ameniya 1980). Water-soluble rather than oily contrast media has to be used in order to keep the suction channel clean and many authorities believe this gives infereior bronchograms. Further, the bronchoscope must be left in the X-ray field during exposure, which leads in time to discoloration of the instrument fibres.

The method can be simply extended in two ways to proceed to full bronchography if required:

1. Removal of the catheter, insertion of a guide wire and, after removal of the bronchoscope, a conventional tracheal catheter can be threaded over the guide wire.
2. Withdrawal of the bronchoscope to the epiglottis and introduction of a soft tracheal catheter through the opposite nares, advancing it under endoscopic control through the vocal cords (Wagner & Paidipaty 1979).

The bronchogram can then be performed as in conventional techniques but with less patient discomfort because of previous anaesthesia for the bronchoscopy.

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PULMONARY ALVEOLAR MICROLITHIASIS WITH AN UNUSUAL RADIOLOGICAL PATTERN

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Summary

We present a case of pulmonary alveolar microlithiasis with an unusual radiological pattern in an anotherwise asymptomatic young woman. It was characterized by a reticulonodular pattern predominantly in the lower lung fields with Kerley B lines. The diagnosis was made by transbronchial lung biopsy. We found an otherwise asymptomatic brother with the same radiological pattern.

Introduction

Pulmonary alveolar microlithiasis is an uncommon disease of unknown aetiology. Sadaba et al. (1980) found 160 previously reported cases. The diagnosis is usually made on the basis of the typical radiological pattern, of a very fine, sand-like micronodulation of calcific density diffusely involving both lungs and most marked in the middle and lower zones (Fraser & Paré 1979; Schoenhals & Fishman 1980). Lung biopsy is usually unnecessary to confirm the diagnosis (Fraser & Paré 1979; Sosman et al. 1957; Thind & Bhatia 1978). We present a case of pulmonary alveolar microlithiasis in an anotherwise asymptomatic young woman. There was a reticulonodular pattern on the radiograph with some areas of honeycombing and Kerley B lines, very unusual findings in this disease. The diagnosis was made by transbronchial lung biopsy. We found an asymptomatic brother with the same radiological pattern.

Case Report

A previously healthy 25-year old woman came to the hospital on 4 November 1977 complaining of headache, nausea, dizziness and fever. The physical examination revealed a temperature of 40 °C, pulse rate 120/min and blood pressure 110/70 mmHg. The pharynx was hyperaemic but the rest of the examination was normal. The packed cell volume was 40%, the white-cell count was 12 200/mm^3, with 73% segmented neutrophils, 18% band forms, 7% lymphocytes and 2% monocytes. The urine sediment was normal. A chest radiograph revealed a bilateral diffuse interstitial reticulonodular pattern without calcific density, predominantly in the lower lung fields, with probable areas of honeycombing and with Kerley B lines (Figs 1, 2). Three days after admission the fever disappeared and the patient decided to leave hospital against medical advice.

Five months later, she came to the hospital with upper gastrointestinal bleeding, probably related to salicylates which she often took. No abnormality was detected on physical examination. The packed cell volume was 42%, the white-cell count was 9800/mm^3 with a normal differential count and the erythrocyte sedimentation rate was 12 mm/hour. Liver function tests, serum creatinine and serum proteins were normal, as were serum calcium and phosphorus. There was no proteinuria and the urine sediment was normal. Serum iron and a sweat test were normal and a test for antinuclear antibodies was negative. The tuberculin skin test (PPD, 5 TU) showed an induration of 15 mm at 48 hours. Acid-fast bacilli were not found in the sputum and Lowenstein's culture was negative. An ophthalmoscopic examination was normal. The chest radiograph was similar to the one taken five months before. Tomography showed the same radiological pattern: mediastinal structures and bony thorax appeared normal and no cardiomegaly or lymphadenopathy were found. An electrocardiogram and arterial blood gases were normal. Films of the abdomen and the skull were normal. Pulmonary function tests, including vital capacity (VC), forced expiratory volume in one second (FEV_1), the FEV_1/VC ratio, the airway resistance and the diffusing capacity for carbon monoxide were normal. A transbronchial lung biospy was performed. Histopathological examination showed the occupation of the alveoli by microliths, a basophil amorphous material with calcium deposits and concentric laminations. There was a little mononuclear infiltrate and fibrosis in the alveolar walls of the neighbouring area (Fig. 3).

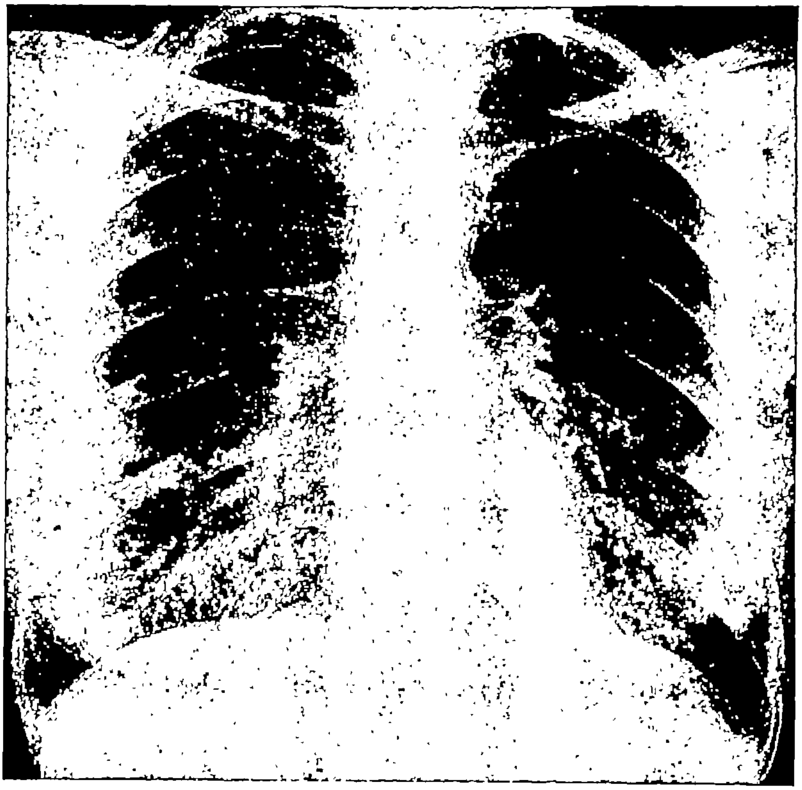

Fig. 1. Chest radiograph showing a reticulonodular pattern, predominatly in the lower lung fields, with possible areas of honeycombing

Her parents, her 11 brothers and her two children underwent chest radiographs, and we found an otherwise asymptomatic 21-year-old brother with the same radiological pattern (Figs 4, 5).

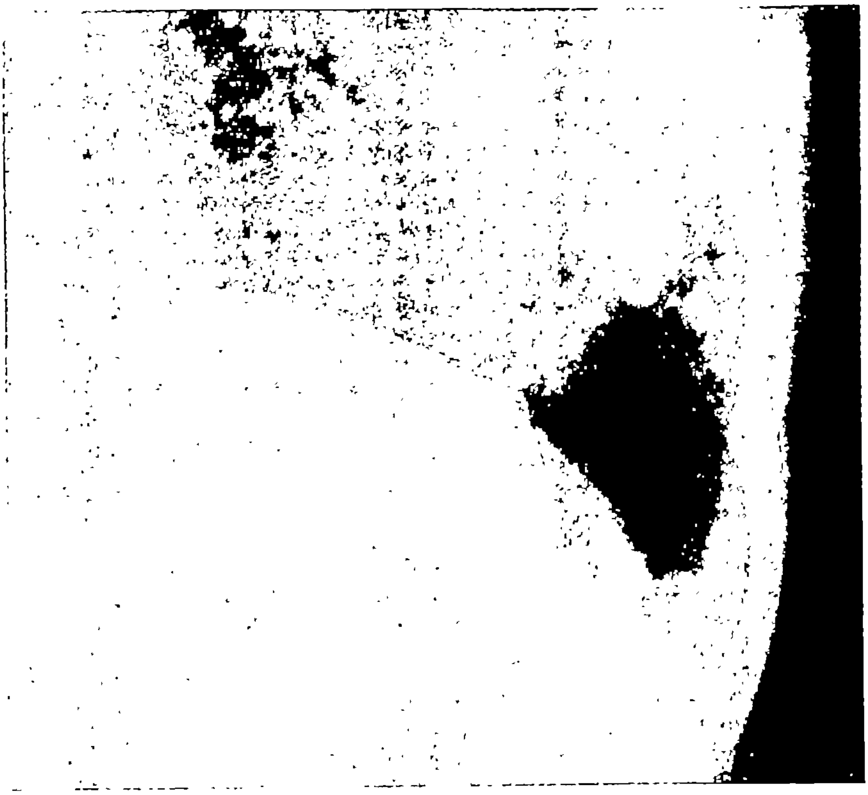

Fig. 2. Enlargement of base of left lung, showing Kerley B lines

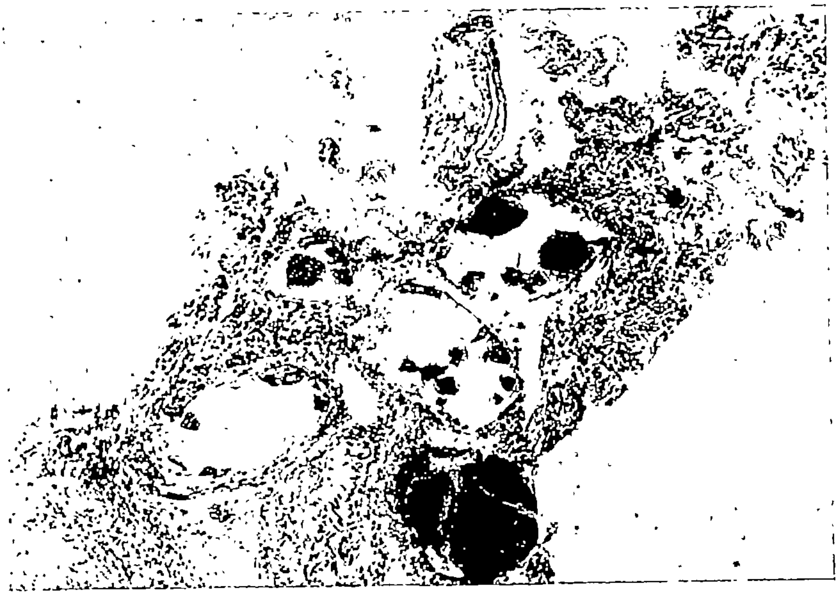

Fig. 3. Microscopical section of the lung biopsy specimen showing typical microliths in most of the alveoli

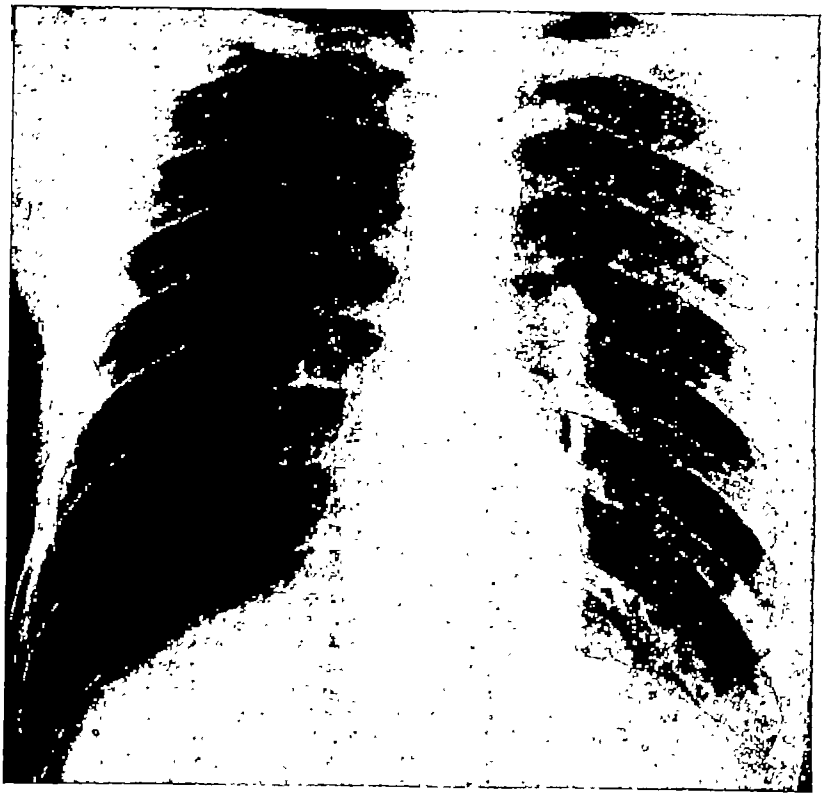

Fig. 4. Chest radiograph of the brother of the patient described showing a similar appearance

DISCUSSION

The diagnosis of pulmonary alveolar microlithiasis is well established in our case as transbronchial lung biopsy showed the typical appearance of microliths within the alveoli. Their chemical analysis reveals chiefly calcium and phosphorus and no silicon or iron; they are 0.01–3.0 mm in diameter and have a structure of onion-like concentric layers. In the later stages interstitial fibrosis can appear with thickening of the alveolar walls (Fraser & Paré 1979; Schoenhals & Fishman 1980). Although microliths can be found in the sputum, they are not diagnostic and Tao (1978) found that the sputum of 26% of patients with chronic obstructive pulmonary disease contained microliths.

Although the aetiology of the disease remains obscure, a familial occurrence has been noted in more than half the reported cases (Sosman et al. 1957). The possibility of a congenital error of metabolism at the level of the alveolar surface membrane has been suggested (Sosman et al. 1957; Balikian et al. 1968). Others have suggested that this condition is a result of an exudative process with subsequent calcification (Hotchi et al. 1970) or is the result of an inflamatory process, probably hyperimmune (Barr & Ferguson 1963).

The characteristic picture of pulmonary alveolar microlithiasis on the chest radiograph shows a very fine, sand-like micronodulation of calcific density, diffusely involving both lungs, usually most marked in the middle and lower zones, that gives the radiograph a 'snowstorm' appearance. Pleural thickening and air broncogram have been described, and the 'black' pleural line is the result of the contrast between the density of the lung parenchyma and the ribs. The diagnosis is usually made during a screening chest radiograph or in an intercurrent illness, as in our patient, on the basis of the typical radiographic pattern and, in most cases, a striking dissociation between the radiographic appearances and the clinical state (Fraser & Paré 1979; Schoenhals & Fishman 1980). The appearance is so typical that it is unnecessary to confirm the diagnosis by means of lung biopsy (Sosman et al. 1957; Thind & Bathia 1978; Fraser & Paré 1979). Sometimes, the micronodular pattern does not have calcific density and other processes that produce a miliary pattern on the chest radiograph must be considered (Saputo et al. 1979). Our patient had a chest radiograph with a reticulonodular pattern, some areas of honeycombing and Kerley B lines, which is very unusual in this disease. Such an interstitial pattern has also been described by Balikian et al. (1968) and Vidal Pla et al. (1975). Pulmonary alveolar microlithiasis is usually not included in the differential diagnosis of this appearance (Felson 1966; Reeder & Felson 1975).

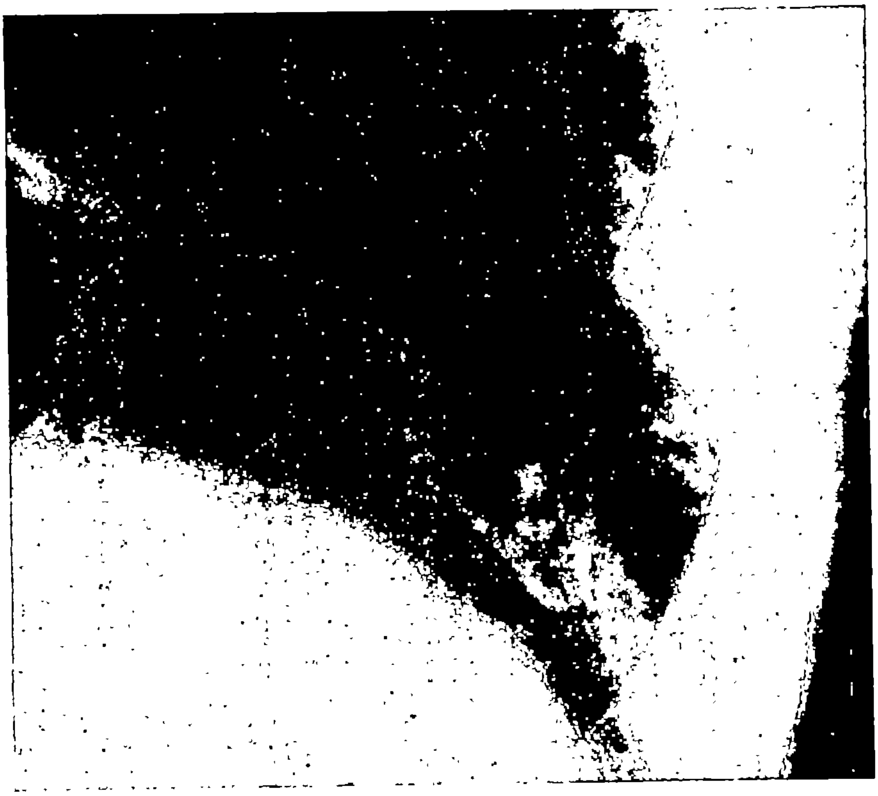

Fig. 5. Enlargement of Fig. 4 showing Kerley B lines

There is usually a slow and asymptomatic clinical course and when symptoms finally do occur, they usually consist of a non-productive cough and dyspnoea on exertion. Gradually, over years respiratory insufficiency, cor pulmonale and death may ensue. In the later stages alterations in pulmonary function can appear, with first a restrictive pattern and decreased diffusing capacity and latter ventilation-perfusion abnormalities (Fuleihan et al. 1969). Treatment for pulmonary alveolar microlithiasis is only supportive.

Other cases of pulmonary alveolar microlithiasis may present this radiological pattern and this disease must be kept in mind in the differential diagnosis of a reticulonodular pattern, with Kerley B lines. Lung biopsy may be required to establish a definite diagnosis.

ACKNOWLEDGEMENTS

We are grateful to Dr L. Camacho for the histopathological study of the lung biopsy specimen and Dr A. Marin and Dr M. Sasal for their collaboration in the preparation of this paper.

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Short Communication

FLEISCHNER'S LINES—A MODEL?

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Horizontal linear shadows above the diaphragm have been the subject of contention for many years (Fleischner 1936; Fleischner et al. 1941; Simon 1970). Some hold that these lesions are bronchial in origin, others that they are essentially vascular in origin, while in the case examined by Fleischner a zone of airless alveoli with no particular relation to a vessel or bronchus was found. A simple model of the lung has been constructed and subjected to compression by a simulated diaphragm.

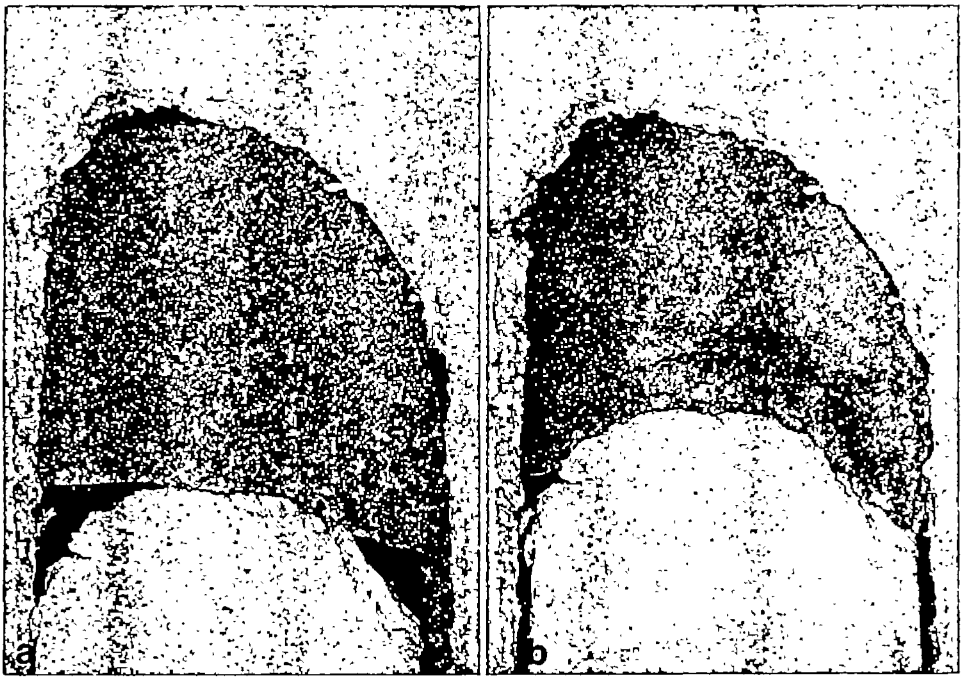

Fig. 1. A model of the lung with a piece of polythene to simulate the diaphragm

A sheet of polystyrene was cut to represent the thoracic cage in section and within this was placed a section of plastic foam to represent lung. A second curved section of polystyrene was positioned to simulate the diaphragm and to compress the 'lung' (Fig. 1*a*). If new plastic foam was used to represent lung tissue, compression by the elevated 'diaphragm' led to even decrease in the volume without any localized deformation. Plastic foam which had been soaked in a water-soluble contrast medium and allowed to dry, and which consequently was less compliant, showed basal 'supradiaphragmatic' horizontal line shadows (Fig. 1*b*) when compressed in a similar manner.

It is tempting to speculate that a similar process can occur in life. Compression by the diaphragm of lungs less compliant than normal because of the presence of oedema or infection could lead to areas of atelectasis which would not necessarily be confined to one lobe and could cross fissures; loss of surfactant may contribute to their persistence. Vessels entering these areas may be more susceptible to thrombosis with consequent extension of the lesion to involve the pleura as postulated by Simon. Further development of and contributing to persistence of the plate-like lesions might be the result of deformation of the bronchi within the primary lesion with peripheral collapse and inspissation of secretions in the bronchi. Trapnell (1980) has observed by tomography a patent bronchus the lumen of which became obliterated on entering a typical area of 'plate atelectasis'. The variable and often short time-course of the lesions could be explicable depending upon the presence or absence of a vascular or a bronchial lesion in addition to the primary compressive atelectasis.

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MULTIPLE CEREBRAL ABSCESSES IN AN ADULT WITH CYSTIC FIBROSIS

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Cerebral abscess is a well recognized complication of suppurative lung disease (Collis 1944) but has only rarely been described in patients with cystic fibrosis (Duffner & Cohen 1979; Fischer et al, 1979). Surgical drainage has usually been used in the management of the condition but can carry a high mortality (Samson & Clark 1973). We report here a case of successful medical treatment of multiple cerebral abscesses in a young women with cystic fibrosis.

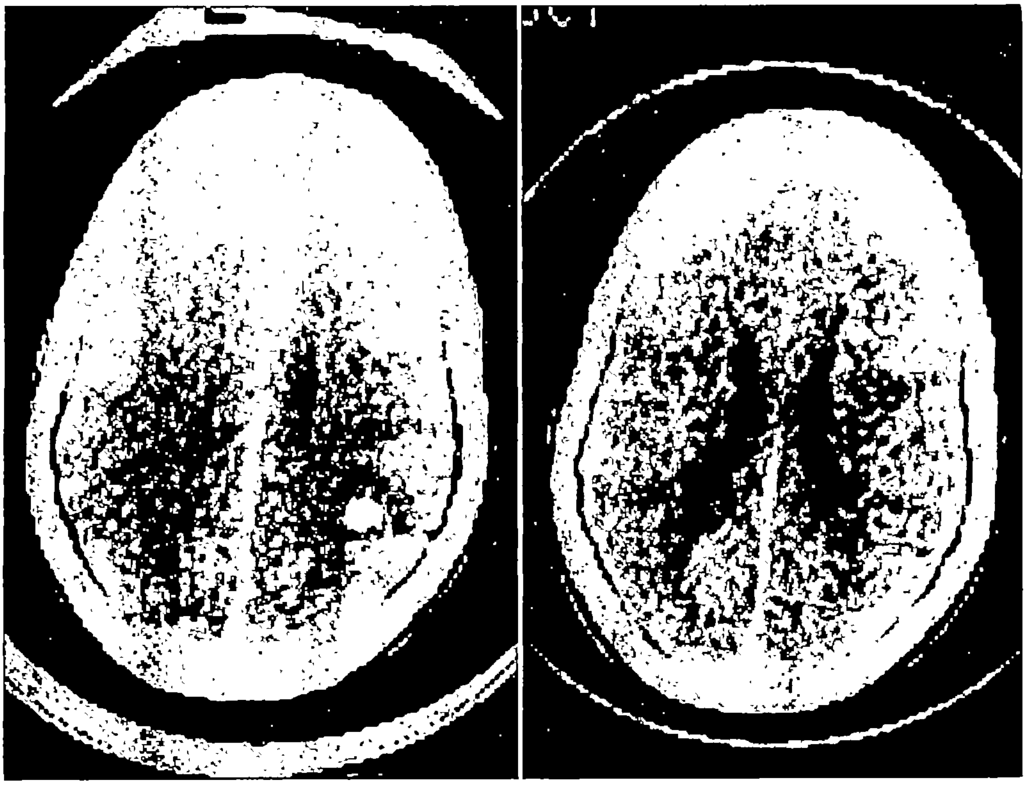

Fig. 1. CAT scan on presentation (*left*) and six weeks later (*right*) showing resolution of the abscess in the right occipital lobe

Case Report

The patient was a woman aged 22 who had first come under the care of this hospital when aged 17. At the age of six she had been diagnosed as suffering from cystic fibrosis, with raised sweat sodium levels, following the development of steatorrhoea. She remained well until the age of 18 when chest infections necessitated admission to hospital on two occasions. At the age of 22, she had three severe chest infections, requiring in-patient treatment. On the third occasion she had respiratory failure (arterial blood gases: $P\text{O}_2=6.4$ kPa, $P\text{CO}_2=7.1$ kPa and $\text{pH}=7.30$) and right heart failure (ECG showing right ventricular strain and an axis of +120°) with a severe restrictive/obstructive defect of ventilation ($\text{FEV}_1=0.4$ litres, $\text{FVC}=0.8$ litres). Sputum culture grew *Proteus mirabilis* which was sensitive to cephazolin. She was treated with physiotherapy, salbutamol by inhalation, ampicillin 500 mg six-hourly and cephazolin 500 mg six-hourly intravenously and diuretics. She improved and was discharged, apyrexial, 10 days after admission. Four days later she was readmitted having had two *grand mal* convulsions. On examination she was well oriented and afebrile but had slight weakness of the right arm and leg with a right extensor plantar response. Computerized axial tomography (CAT) of the brain revealed three focal lesions compatible with cerebral abscesses: one in the left frontal region, a second in the right occipital region (Fig. 1 left) and a third in the right posterior fossa. She was treated with intravenous ampicillin 1 g six-hourly and flucloxacillin 500 mg six-hourly and metronidazole 400 mg eight-hourly and oral phenytoin 100 mg eight-hourly. Her neurological signs improved and subsequent CAT scans showed gradual but complete resolution of the intracranial abscesses (Fig. 1 right). Two years later, she remains well and has no residual neurological defect.

DISCUSSION

Until the advent of antibiotics, cerebral abscesses complicating suppuration in the thorax were invariably fatal (Collis 1944). Since that time there has been only a slight fall in the incidence of all cerebral abscesses (Garfield 1969) but the mortality has fallen to between 30 and 60% (Samson & Clark 1973). However cerebral abscess associated with pleuropulmonary infection still carries a high mortality, given as 66% in one series (Garfield 1969). Cerebral abscess in cystic fibrosis has been reported in only four patients (Duffner & Cohen 1979; Fischer et al. 1979). All were adults with severe lung involvement, two of whom had pulmonary hypertension, with or without cor pulmonale, all features which were seen in our patient. The four previous patients were treated by antibiotics combined with surgical drainage, but our patient is apparently unique in having survived after treatment with antibiotics alone. Culture of the abscess from the four other cystic fibrosis patients (Duffner & Cohen 1979; Fischer et al, 1979) grew mouth commensals but no pulmonary pathogens. This casts doubt on the theory of Collis (1944) that cerebral abscesses associated with pleuropulmonary infection are caused by emboli reading the brain by retrograde flow in the vertebral veins. In our patient the delay between apparent clearing of the chest infection and presentation of the cerebral abscess implies that the intitial antibiotic therapy may have sterilized the abscess without causing resolution. More patients with cystic fibrosis are now reaching adulthood because of better physiotherapy and antibiotics and as a result, rare complications such as cerebral abscess may now become more frequent.

ACKNOWLEDGEMENT

We thank Professor T. J. H. Clark for permission to report this case.

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BOOK REVIEWS

Metabolic Activities of the Lung: Ciba Foundation Symposium 78

Amsterdam: Excerpta Medica. 1980. Pp. x+401. Price DFl 136

This volume sets out an account of the events at a Ciba symposium held in February 1980 at which a group of experts presented recent work and discussed the meaning of the work amongst themselves. It therefore offers a vignette of the current state of the art in respect both of methods and thought. The relationship between function and ultrastructure, to which much effort is being directed is set out in the opening chapter, which serves to illustrate how long will be the journey on which we are embarked.

Two broad classes of substance are currently under study in the lung, derivatives of arachidonic acid and the peptides. The substance of greatest interest in the former group is prostacycline and this was discussed by many contributors. The role of pulmonary vascular endothelium as its source raised many questions about its role and most remain unanswered. The methods in this area are still imprecise, involving superperfusion and platelet aggregation; it would appear that better quantitative methods are now required. A step forward was the structural elucidation of slow-reacting substance as a derivative of tetraenoic acid. The role and position of receptors and receptor sites received much attention.

The role of prostaglandins in the aetiology of bronchial asthma is still a matter for discussion, but hard evidence appears difficult to come by. As an example, the disparate effects of these compounds on airway function has been explained by postulating three quite different types of receptor. Endocrines are involved in many metabolic processes and insulin may be an important regulator of lung function. An interesting idea was that the metabolic activity of the lung is used to determine the biochemical constituents in arterial blood and hence to regulate the whole of peripheral metabolism.

The role of peptides includes that of convertin, on which there was a historical survey, and there was reported a new pulmonary peptide which resembles the intestinal VIP. The mechanics of action of peptides poses some paradoxes, and a limiting factor is now seen as membrane transfer rate, perhaps based on dipeptidyl carboxydipeptidase located on the luminal surface of epithelial cells. The effect of steroids on fetal development and the protection of the premature infant from the respiratory distress syndrome was again discussed.

The information contained in these papers, and in the ensuing discussion, offers a valuable summary of the present situation in pulmonary metabolism, which is moving with great rapidity.

G. Cumming

Disorders of the Respiratory System

Gordon Cumming and Stephen J. Semple

Oxford: Blackwell Scientific. 1980. 2nd edition. Pp. xii+616. Price £32 cloth, £18 paper

This book is written with the needs of the preclinical student of pulmonary physiology in mind, though it is primarily directed towards those receiving training in respiratory disease at both the undergraduate and postgraduate level. Consequently almost one-third of the text is devoted to pulmonary physiology, after a brief introductory glance at the morphometry of the lungs with an apparent disregard for the gross anatomy of these organs. The larger, second part is devoted to the theme indicated by the title of the book: disorders of the respiratory system.

Owing presumably to the constraints set by the authors in addressing such a wide readership, there is a lack of balance in the contents of different sections. Thus, gas mixing in the lungs is described in 20 pages of text whilst bronchial asthma is dealt with in 14. The chapter on respiratory insufficiency and failure, which is 44 pages long, contains unnecessary detail on mechanical ventilators and includes two pages of diagrams showing complications associated with tracheostomy tubes. By contrast, the common and important clinical problem of pleural effusion receives cursory attention, and no guidance at all is given on the technique of pleural aspiration and biopsy. Whilst the various drugs available for the chemotherapy of tuberculosis are listed, the actual advice given for its treatment is out of date. (In this chapter one expected the spelling error of Ziehl-Neelsen, seen in the 1st edition, to have been corrected. Elsewhere, the eponymous adjectives in 'Thebesian veins' and 'Mendelson's syndrome are also incorrectly spelt).

The authors will perplex even if they do not confuse some of their readers when they refer to a table that does not exist, as on p. 31; provide an illustration as unconvincing as that on p. 88; state that a figure (6.6) is reproduced at the end of the book for future use in plotting 'acid–base' data when, in reality, a quite different diagram is provided; state that arterial desaturation can be produced by a large arteriovenous difference in the peripheral circulation (p. 208); use obsolescent terminology in their description of pulmonary adventitious sounds; say that the preservation of gas transfer is a characteristic of emphysema (p. 220); and inform the student *after* he has read several pages of text devoted to the chest radiograph that this investigation will be discussed subsequently.

It is perhaps wrong, when reading a book, for a reviewer to keep making mental comparisons between the one he is reviewing and other contemporary texts on the same subject. But it cannot be helped. There are smaller monographs available for undergraduate medical students and bigger texts for the postgraduate who needs more detailed information, and this volume unfortunately seems to fall between these two stools.

T. B. STRETTON

An Introduction to Tuberculin Testing and BCG Vaccination

A. N. Shashidhara

Bangalore: National Tuberculosis Institute. 1981. Pp. xvi + 120. Price £3

This is an interesting volume, written as a guide to non-medically trained staff working as technicians using tuberculin testing and BCG vaccination on a wide scale. As an introduction it includes a fair amount of background information about tuberculosis, which is perhaps a little over-simplified for the medical or nursing reader. The account of the development, preparation and use of tuberculin is interesting and detailed; the emphasis is particularly on Mantoux testing. I do not think it would be a particularly helpful practical manual for the establishment of a tuberculin testing programme in a developed country, but it provides an enjoyable and informative survey of its subject.

MARTIN W. MCNICOL

Surgery of the Lung

H. Christian Nohl-Oser, Rudolf Nissen and Hans Wilhelm Schreiber

Stuttgart: Georg Thieme. 1981, 2nd edition. Pp. x + 190. Price DM 198

A new monograph on surgery of the lung is a rare event in the history of thoracic surgery. This volume purports to be a successor to the first illustrated monograph on lung resection in German, published by Lezius in 1973. In fact it is a completely new volume written almost entirely by Mr Nohl-Oser, with an excellent and comprehensive chapter on anaesthesia in thoracic surgery by Dr Ann Triscott, Consultant Anaesthetist to the Cardiothoracic Unit, Harefield Hospital, England.

Mr Nohl-Oser has had a very wide experience of surgery of the lungs and bronchi and has himself made original observations on the lymphatic drainage of the lung and on mediastinoscopy. It is, therefore, of considerable value to practising cardiothoracic surgeons to be able to read Mr Nohl-Oser's views on how to undertake each step in a particular operation, how to avoid pitfalls and the management of difficulties, complications and disasters when they are encountered. This is all of interest to the established thoracic surgeon, but is it for him that the book was written?

Mr Nohl-Oser in his preface says that his objective is the teaching of the finer details of operative technique to young surgeons. I am not sure that the book is successful in this respect for two reasons. The first is that the number and quality of the illustrations is not sufficient to allow the tyro who has never performed the operation previously to grasp all the steps involved. It is true that the text gives a very full description but in my experience surgeons do not expect to learn *how* to operate from a book. They do, however, need to refer to a book of illustrations in order to memorize the steps involved in an operation. It is a pity that the book is unlikely to be used in the way that the author hopes since every page is packed with valuable advice.

There are of course many matters about which one cannot expect to obtain general agreement, e.g. not many thoracic surgeons would consider that the appropriate prophylactic chemotherapy was a five-day course of ampicillin. Then again, although the volume is dated 1981, there is no mention in the section on postoperative analgesia of the use of the fentanyl drip or of intrathecal morphine. Induced hypotension for the reduction of blood loss in difficult decortication procedures is not mentioned. And the statement 'prophylactic digitalizing is commonly performed in patients above a certain age in lung resection' is vague to the point of unhelpfulness, as well as lacking in elegance.

The mechanical stapler has revolutionized many of the practical steps in lung surgery in recent years, but it is mentioned only once in this volume, mainly in connection with wedge excision of the lung to prevent postoperative air leak. Alas, the figure to which one is referred shows a suturing technique. There is no mention of the value of the stapler for the closure of arteries, veins and bronchi.

Nevertheless, this book is a remarkable demonstration of the skill and experience of one surgeon and enshrines in prose of great clarity, details which may soon be forgotten, such as the methods of removing the individual segments of the lungs. Every thoracic surgeon would enjoy reading this book and could not fail to benefit by picking up some of Mr Nohl-Oser's pearls.

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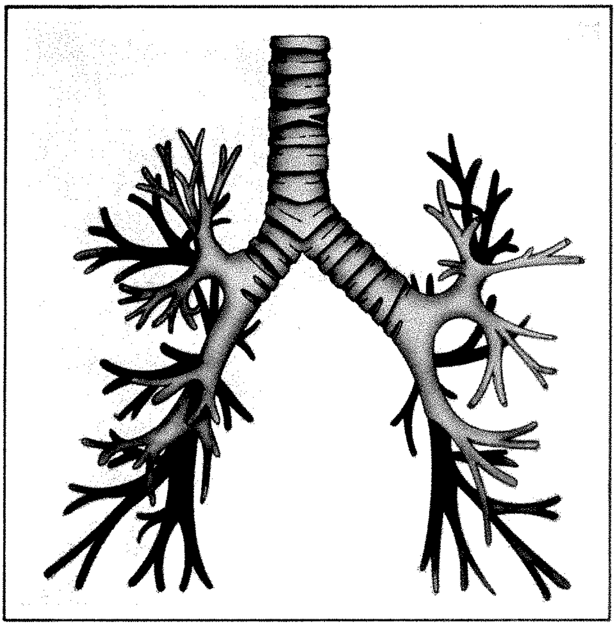

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Br. J. Dis. Chest (1982) *76*, 105

Does the Lung Work?

4. WHAT DOES THE TRANSFER OF CARBON MONOXIDE MEAN?

N. J. H. Davies

Department of Physiology, University of California San Diego, USA

Introductory Remarks
By David Denison

Two of the previous articles in this series, concerning gas exchange in the lung, have been leading to the views summarized in the figure on p. 106, namely that:

i. Convection carries gas into the lung, shortening the diffusion path in the gaseous phase and greatly increasing its cross-sectional area. Any failure of convection lengthens the diffusion path and reduces its area.

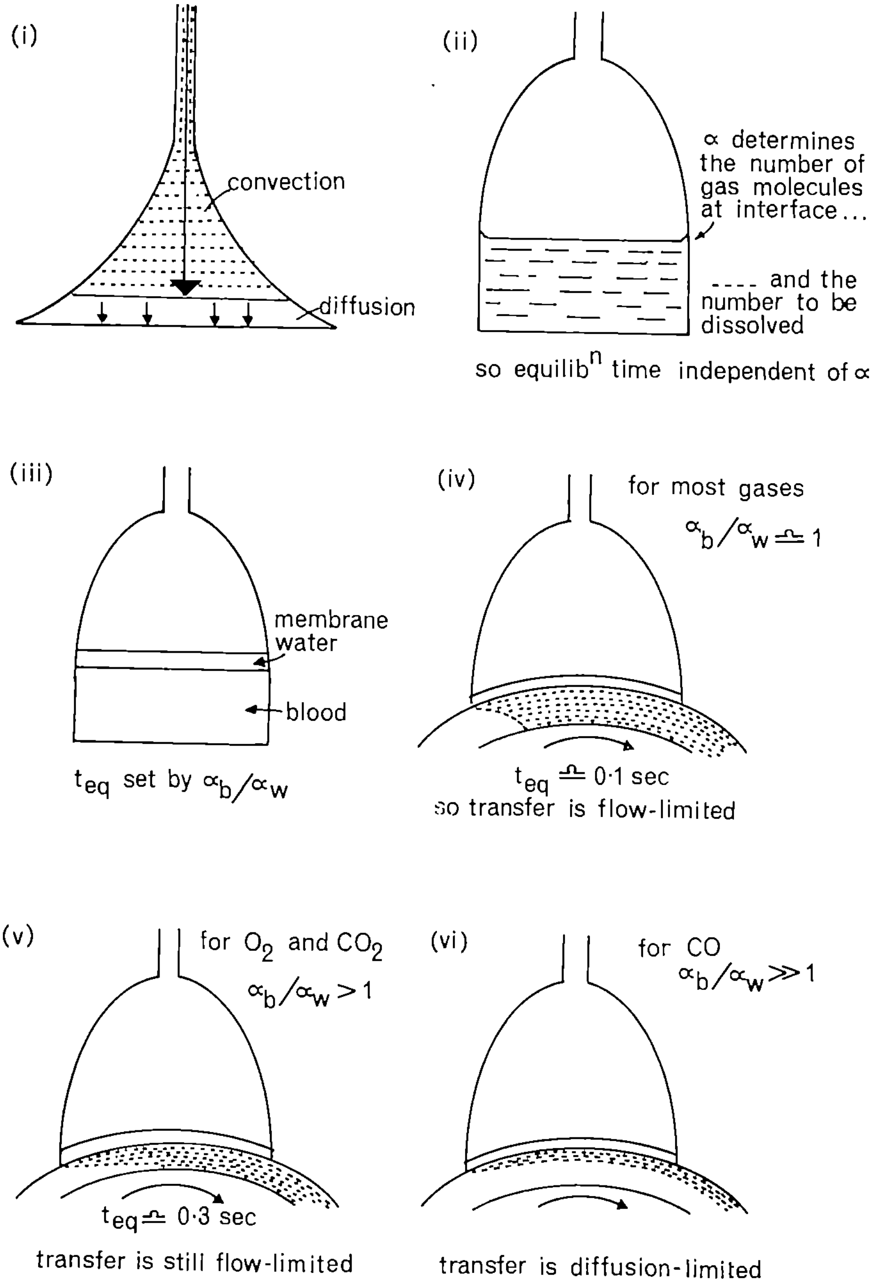
ii. In a simple gas–fluid exchange system, the time needed for gas and fluid to equilibrate is independent of the gas's solubility in the fluid, since doubling the solubility not only doubles the amount needing to be dissolved but also doubles the number of molecules available for diffusion through the fluid.

iii. In a system where gas must diffuse through one static fluid (e.g. membrane water) to reach another (e.g. blood), the equilibration time is proportional to the solubility in blood and inversely proportional to the solubility in membrane water, i.e. it is determined by the ratio α_b/α_w.

iv. For most inert gases, that ratio is quite close to 1. These gases equilibrate in the first 10% or less of the time taken by a red cell to transverse the capillary of the lung. The latter is about 1 second at rest and 0.3 second on exertion.

v. Oxygen and CO_2 are substantially more soluble in blood than in membrane water and so take rather longer to equilibrate, (say 0.3 second) but even on exertion, in normal lungs they still complete the process within the red cell's passage through the lung. Their exchange is determined by blood flow.

vi. Carbon monoxide is much more soluble in blood than water and so cannot equilibrate within the transit time of a red cell through a pulmonary capillary. Its exchange is therefore diffusion-limited. However, it is also restricted by the rate at which CO combines with haemoglobin in the red cell.


(i)
convection
diffusion
(ii)
α determines the number of gas molecules at interface...
.... and the number to be dissolved
so equilib^n time independent of α
(iii)
membrane
water
blood
t_eq set by α_b/α_w
(iv)
for most gases
α_b/α_w ≏ 1
t_eq ≏ 0·1 sec
so transfer is flow-limited
(v)
for O₂ and CO₂
α_b/α_w > 1
t_eq ≏ 0·3 sec
transfer is still flow-limited
(vi)
for CO
α_b/α_w ≫ 1
transfer is diffusion-limited

Over the past few years, as the following article suggests, our understanding of the factors that determine CO transfer in the lung (D_LCO and KCO) has changed considerably. It is timely to reconsider what these familiar indices of lung function mean.

INTRODUCTION

The first article in this series demonstrated some surprising pitfalls in the interpretation of a simple and common test of lung function. The example cited was the measurement of volume by inert gas dilution, and here that thesis is extended to the measurement of carbon monoxide transfer (T_{L}CO).

Although conceived as an index of the barrier that the alveolar–capillary membrane presents to gaseous diffusion, it is now clear that the story is much more complex. This account traces how important changes have become necessary in the interpretation of the test, compares the different methods of measurement and so tries to help the clinician understand its significance.

WHY CARBON MONOXIDE?

The most important function of the lung is to transfer gas between air and blood and the T_{L}CO is meant to be a direct measure of its ability to do so. It is the ***conductance*** of the barrier between alveolar gas and pulmonary capillary red cells. Conductance is a familiar concept when we think of the flow of liquid down a pipe or of electricity along a wire. It is defined as the flow per unit drop in driving pressure and is the reciprocal of the more commonly-used term 'resistance'.

So for the lung:

$$T_{L}x=\frac{\dot{V}x}{P_{A}x-P_{c}x} \tag{1}$$

where $\dot{V}x$ is the flux of gas x across the barrier from alveolar air to capillary blood and $P_{A}x$ and $P_{c}x$ are the mean partial pressures of the gas in these two mediums. $T_{L}x$ is the ***transfer factor*** of the lung for gas x, and is synonymous with D_{L}, the ***diffusing capacity***. This formula can be a useful visual mnemonic of the way in which it is calculated (Fig. 1). The latter term has the disadvantage of implying that it is concerned solely with diffusion (which, as we will see, is not the case); on the other hand it has the advantage of stressing the measure of capacity and therefore of reserve available to the lung.

The processes of ventilation and diffusion in the gas phase that bring the inspirate up to the alveolar–capillary membrane are considered in another article. However, the uptake of any gas by the lung is not affected only by T_{L} but also by the flow of blood that carries it away. Indeed, if equilibrium is complete between alveolar gas and pulmonary capillary blood then gas uptake will be limited solely by blood flow, as is normally the case for oxygen.

This does not prevent us using oxygen to measure T_{L} for the most important respiratory gas, and indeed such information would be of the greatest interest. However, the final loading of oxygen in any alveolus normally takes place on the flat part of the dissociation curve and results in a relatively large change in the alveolar–capillary partial pressure gradient. The uncertainty over the final value of this gradient may take a precise estimate of its mean value (and hence T_{L}) near-impossible. A 0.012 kPa (0.09 torr) error in end-capillary PO_2 can cause nearly a 100% error in calculated $T_{L}O_2$ (Comroe et al. 1962)! The classical method for the determination of $T_{L}O_2$ (Lilienthal et al. 1946) is a complex two-stage procedure breathing air and then a hypoxic mixture which only partially circumvents these problems and is little used in clinical laboratories today.

So in order to obtain information about the blood–gas barrier we are forced to move away from the physiological gas oxygen and to use carbon monoxide. Carbon monoxide is so avid for haemoglobin that its partial pressure in blood can be considered unaltered as it is loaded throughout the capillary. So P_c can be put equal to the mixed venous tension (and assumed to be zero in a subject not recently exposed to carbon monoxide) and the most difficult term in the above equation is neatly side-stepped. A corollary is that, in contrast to oxygen, the uptake of carbon monoxide is determined only by the rate at which it can move from alveolar air into combination with haemoglobin, and not by blood flow.

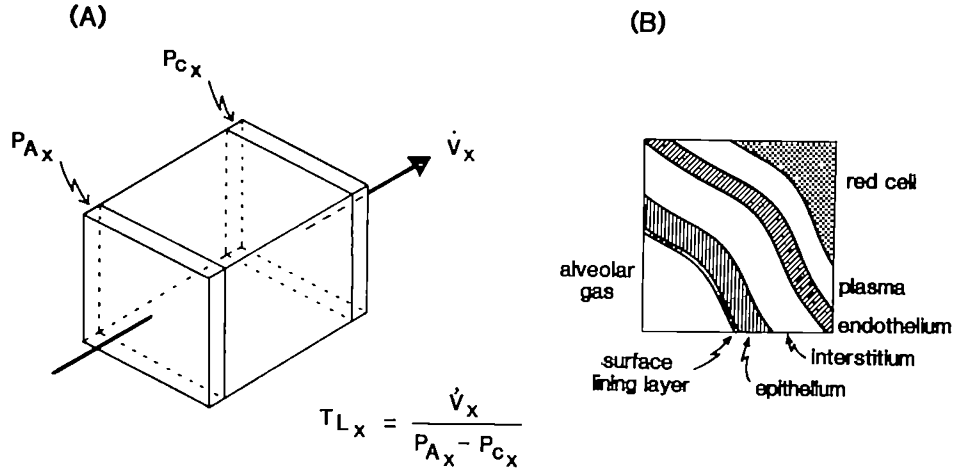


Fig. 1. A, The simplest view of uptake of gas x by diffusion across the alveolar–capillary barrier and the derivation of its T_L. The partial pressures of x in each surface of the barrier are taken to be those in alveolar gas and capillary red cells respectively. B, A more realistic representation of the components of the alveolar–capillary membrane. The thickness of each layer is drawn in approximate proportion to the barrier it presents to diffusion. The harmonic mean thickness of the membrane is around 0.6 μm, although the minimum thickness may be only 0.15 μm

How the Use of Carbon Monoxide has Evolved

Conventional views

It is interesting to sketch the history of carbon monoxide in respiration as it provides an example of the evolution of a useful clinical test out of 'pure' physiological research. At the turn of the century both Bohr (1891) and Haldane (Haldane & Smith 1897) believed that oxygen was actively transported across the alveolar–capillary membrane rather than moving by diffusion alone. They saw the lung as a secretory organ.

Bohr's student August Krogh and his wife Marie developed methods for the precise measurement of gas tensions in blood with which they were to disprove this secretory theory. It was Marie Krogh (1915) who showed that the remarkable extent and thinness of the membrane were normally enough to account for the uptake of oxygen. In doing so she made the first estimate of T_L using carbon monoxide, 'an essentially indifferent gas', and derived the T_{LO_2} on the basis of known differences in diffusivities of the two gases through aqueous solutions. Although she did make measurements on patients with various lung diseases her primary objective was to answer a basic physiological question. Both Bohr and Haldane had defined the unusual properties of carbon monoxide, but it was Krogh who so cleverly exploited its curious avidity for haemoglobin. Otherwise the definition of the lung's diffusing properties would have needed a mixed venous blood sample, which was not possible at the time.

Comroe (1975) has pointed out that despite this early measurement of such an important parameter of lung function it was over 35 years before the test was used much again. The infra-red carbon monoxide analyser pulled the technique out of the research laboratory into clinical medicine and in the 1950s the determination of $T_L$co was given a firm theoretical and practical footing (Forster et al. 1955).

Soon afterwards Roughton and Forster (1957) showed that movement of carbon monoxide into blood was not determined simply by the properties of the alveolar–capillary membrane. This was only true for movement into capillary plasma. The final step through the red cell membrane and into combination with haemoglobin turned out to be unexpectedly slow. This was treated as if a second barrier to diffusion was placed in series, whose conductance could be given the value $\theta \times V_c$, where θ is the rate at which carbon monoxide is taken up by unit volume of blood per unit partial pressure head, and V_c is the volume of blood in the pulmonary capillaries. So now the T_L that had been measured by Krogh over 40 years earlier was represented as the sum of two conductances in series, that of the membrane only (D_M) and that for the chemical reaction rate ($\theta \times V_c$). These conductances are summed thus:

$$\frac{1}{T_L} = \frac{1}{D_M} + \frac{1}{\theta \times V_c} \qquad (2)$$

Carbon monoxide reacts more slowly with haemoglobin if the oxygen partial pressure is high and this was exploited by Roughton and Forster (1957) to measure D_M and V_c separately in man. They determined T_L at several levels of inspired $P\mathrm{O}_2$ and plotted the relationship between $1/T_L$ and $1/\theta$ (Fig. 2), assuming that their careful measurements of θ made at various oxygen tensions in vitro could be applied in vivo. The equation above shows that this relationship should be a straight line whose slope gives V_c and whose intercept on the ordinate gives D_M. It transpired that the barrier to carbon monoxide movement provided by the finite reaction rate was roughly equal to that imposed by the alveolar–capillary membrane.

Thus the measurement of $T_L$co had turned from an estimate of the diffusivity of a gas across the alveolar–capillary membrane into a test that also gave information about the blood in pulmonary capillaries. By the same token it gave scope for the misinterpretation of abnormalities seen in patients, and it became important to realize that a change in T_L did not necessarily mean a change in membrane properties, but could also result from an alteration to capillary blood.

Recent developments

A remarkable recent paper (Burns & Shepard 1979) gives evidence for pushing the pendulum even further away from the importance of the membrane component of T_L. These workers, using an isolated lung preparation, provided exactly those conditions that make carbon monoxide the gas of choice to measure T_L, but for oxygen. That is, they reduced the capillary blood P_{O_2} everywhere to near-zero. They achieved this curious state by adding sodium dithionite to the perfusing blood, which (just like haemoglobin for carbon monoxide) is extremely avid for oxygen. In addition the reaction rate of oxygen with this substance is very fast and can be assumed not to limit the rate of transfer of oxygen into the capillary blood.

In this way, they measured the membrane component (D_M) directly and found it to be very high, even comparable with morphometric estimates (see below), and over ten times higher than that measured by conventional techniques. The alveolar–capillary membrane appeared to be a very feeble barrier to the diffusion of oxygen.

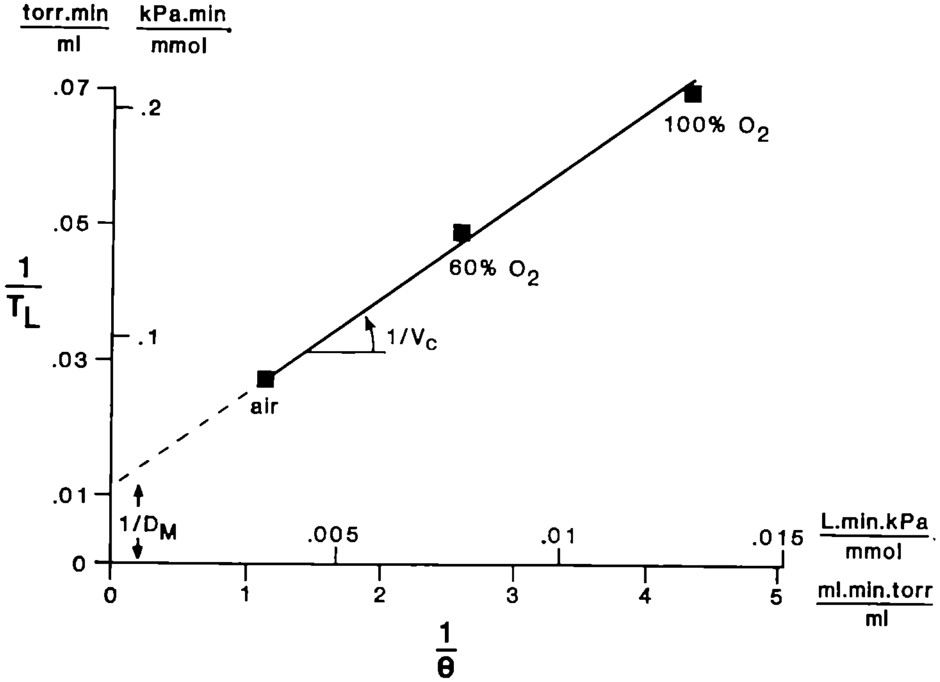


Fig. 2. An example of the measurement of T_L at three different inspired oxygen concentrations. $1/T_L$ is plotted against $1/\theta$, where θ is the reaction rate of carbon monoxide with haemoglobin at the various mean capillary oxygen tensions. Equation (2) indicates that the ordinate intercept is $1/D_M$ and the slope of the line gives $1/V_C$

These results should naturally be treated with caution. It is possible, for instance, that some sodium dithionite in the perfusate did not stay confined to the blood vessels, but leaked into the interstitial space. This would abolish the P_{O_2} gradient across the endothelium and so measure only the epithelial component of the diffusion barrier. Nonetheless, if confirmed, these experiments would impose a new caveat on the interpretation of T_L.

In the last few years Gurtner and co-workers at Baltimore (Gurtner 1980) have proposed that there may after all be some active transport of both oxygen and carbon dioxide across the alveolar–capillary membrane. This evokes an echo of the controversy at the turn of the century between Bohr, Haldane and Krogh, and would force a different way of looking at $T_{L}CO$.

The evidence for active CO transport is based on two groups of experiments. In the first, a decrease in T_LCO has been observed with increasing alveolar *P*CO (Ayash et al. 1978), suggesting the presence of a 'carrier' that becomes saturated above carbon monoxide concentration of about 0.05%. The Baltimore workers have also observed a rapid initial removal of carbon monoxide from alveolar gas (analagous to the early movement of soluble inert gases into lung tissue) that greatly exceeds the amount accounted for by simple solution. It is proposed that this represents the combination of carbon monoxide with its carrier molecules. However these observations have not been confirmed by other workers (Meyer et al. 1981; Rubin et al. 1981).

The other evidence for active carbon monoxide transport is derived from the use of drugs that interact with cytochrome P-450 and implicate it as the carrier. In sheep and dogs the administration of SKF-525A, chemical oxidants or even 100% oxygen for 45 minutes (Sybert et al. 1978) have all appeared to interfere with the facilitated component of carbon monoxide transfer, effects that are not seen in newborn lambs, whose lungs are much poorer in cytochrome P-450. The production of this pigment in sheep has also been stimulated by the volatile anaesthetic agent methoxyflurane, with an associated increase in T_LCO (Burns et al. 1977). In man a single dose of diphenhydramine has caused a 10% drop in T_LCO, possibly by interaction with cytochrome P-450.

However, these drugs are clearly not specific for cytochrome P-450 and this evidence should only be regarded as keeping the hypothesis of active transport alive. It must also be noted that any effect of active transport on measured T_L is most marked at concentrations much lower than those used clinically (0.02% versus 0.3%), and that at the latter levels the facilitated component of carbon monoxide transfer would amount to less than 10% of the total.

Gurtner's group have found it more difficult to demonstrate active oxygen transport across the blood–gas barrier owing to the ease with which alveolar–capillary equilibrium is normally reached. In isolated lobe preparations, however, with a high blood flow and low inspired PO_2 to stress diffusion, the administration of various drugs known to bind to cytochrome P-450 caused large increases in the alveolar–arterial PO_2 gradients (Gurtner et al. 1977).

Since the late 1950s increasing interest has been shown in the unevenness of alveolar volume, ventilation, blood flow and diffusing properties that occur even throughout the normal lung. The ways by which disease might distort these patterns further and so impair gas exchange have received special attention (West 1977). This raises the question of whether the apparent T_L might mislead the clinician in the presence of such inhomogeneities. The extent to which this occurs depends on the type of dysfunction and the method used to measure T_L and is discussed below after an outline of the various methods available.

DIFFERENT METHODS OF MEASUREMENT

All methods for determining T_LCO depend on the introduction of carbon monoxide into inspired gas, and the measurement of its rate of movement into pulmonary capillary blood and the partial pressure gradient at which that uptake occurs. Most commonly the approach to equilibrium is observed after a sudden change in inspired *P*CO, as in the single-breath and rebreathing methods, but if carbon monoxide is continually trickled into the inspirate until the alveolar $P\text{CO}$ is constant then the measurement may be made in the steady state. These three methods will be discussed in turn, together with the morphometric studies by Weibel's group.

Single-breath methods

Breathholding. Krogh's original method was to measure the uptake of carbon monoxide during a breathhold. After a sharp inspiration from RV to TLC of a gas mixture containing about 0.3% carbon monoxide an initial expiration of 1 litre was made. The subject exhaled again after a known period of breathholding (10–15 sec) and the alveolar portion of each expirate was analysed for carbon monoxide. From these measurements, and that of lung volume (made independently by hydrogen dilution), $T_{L}\text{CO}$ was readily calculated.

The starting alveolar concentration of carbon monoxide as given by the first expiration, would be misleading if there was any inequality of ventilation throughout the lung. So the method as widely used today adds about 10% helium to the inspirate (Ogilvie et al. 1957). Its dilution, seen on the final expiration, enables both the calculation of lung volume and initial carbon monoxide concentration assuming that the two gases are distributed equally. Thus the first sample is unnecessary and the manoeuvre simplifies to a vital capacity inspiration, a 10-second breathhold and one expiration to collect alveolar gas for analysis.

The equipment needed consists of a carbon monoxide analyser (usually by infra-red absorption), a helium analyser (katharometer), soda-lime to absorb the expired carbon dioxide as both instruments are sensitive to that gas and a spirometer with associated valves and gags to trap the alveolar sample. Naturally several companies present all these together as an attractive unit in which the valve switching and gas analysis is automatic. One of these is described in detail by Cotes (1980). The reproducibility of a single measurement is around 5%.

The lung volume measured by helium dilution may, of course, be quite different from that measured by a separate technique such as body plethysmography, especially in patients. The difference between the two volumes may be a sensitive index of airways disease and the helium volume is a valuable piece of 'free' information.

Slow expiration. Most infra-red analysers respond slowly, but they can be modified to follow changes within a single breath (Cotton et al. 1979). Better, a respiratory mass spectrometer can be used to record the changing concentrations of many gases, including carbon monoxide, during breathing manoeuvres. However, carbon monoxide has the same molecular weight as nitrogen and is used in much lower concentrations, so it is necessary to use a stable isotope such as CO^{18} for the two gases to be distinguished by this instrument (Wagner et al. 1971).

Equipped with such rapidly-responding analysers the uptake of carbon monoxide can be followed during a slow controlled expiration. $T_{L}\text{CO}$ is calculated continuously throughout the breath. This avoids sampling and timing errors that may occur in the breathholding method and, more importantly, yields information about the unevenness of diffusion throughout the lung (in much the same way that the slope of the alveolar plateau for nitrogen gives information about unevenness of ventilation). This technique has been exploited during fibreoptic bronchoscopy when the expirate from any lobe or segment may be analysed (Williams et al. 1979) and measurements of regional T_Lco made under various circumstances (Denison et al. 1980). It appears to have great promise for the more detailed characterization of disordered lung function.

Radioactive isotopes of carbon monoxide have also been used to study the regional variations of T_L in man (Dollery et al. 1960). As with all such investigations the information is strictly topographical and can be difficult to associate with known anatomical units due to overlapping or distortion of lobes and the absence of firm reference points. Also the isotope used (CO^{15}) is extremely short-lived and so available only close to a cyclotron.

Rebreathing methods

The uptake may also be measured during rebreathing. In this case the subject breathes out to a reproducible lung volume (FRC or RV), inspires a known volume of gas marked with about 0.3% carbon monoxide and 10% helium and rebreathes into a bag for 15–20 seconds. The gas concentrations may be measured in aliquots taken at known times (Kruhoffer 1954), or continuously, by infra-red analysis (Lewis et al. 1959) or by mass spectrometry (Sackner et al. 1975; Adaro et al. 1976). The calculation of T_Lco is essentially the same as that for the breathholding method, as the total gas volume from which carbon monoxide (bag+lungs) is assumed constant and measured by dilution of the helium.

This technique has never become popular in routine lung function laboratories as the manoeuvre is less easy to standardize than the breathhold, is less acceptable to patients and is best performed with rapid continuous analysers which are less readily available. If a patient has such a small vital capacity (<1.3 litres) that he cannot deliver a true alveolar sample free of dead space gas, or if his breathholding time is severely limited (<5 sec), then the single-breath methods cannot be used and rebreathing is probably the method of choice. This is particularly true for the critically ill as the apparatus needed for rebreathing can be reduced to a bare minimum, easily taken to the bedside, and the gas analysis done in the laboratory later (Marshall 1977).

It is interesting to note that changes in helium and carbon monoxide concentrations during each of the three manoeuvres described above are similar (Fig. 3). Yet the amount of information used to derive T_L is very different. The breathholding method in particular is heavily dependent on assumed time courses before the alveolar sample is taken.

Steady state methods

T_Lco can also be determined in the severely ill by measuring carbon monoxide uptake in a steady state. The subject simply breathes normally from a mixture marked with about 0.1% carbon monoxide and after some minutes the amount removed from the inspirate becomes constant. This uptake is calculated from the mixed expired concentration and ventilation in a way analagous to the measurement of oxygen consumption (Filley et al. 1954) and will be most accurate when carbon monoxide uptake is high (e.g. during exercise). To obtain the T_Lco the gas flux must be divided by the partial pressure gradient between alveolar air and capillary blood. Even in this technique, with the considerably longer exposure to carbon monoxide, the blood Pco is assumed to be zero (unless in a smoker), but the mean alveolar value is a difficult parameter to measure.

There are three main ways of estimating P_Aco, which will be described in historical order. Before Marie Krogh devised her single-breath method she and her husband had tried a steady state technique. They computed P_{A}CO from the mixed expired value using the Bohr equation and an assumed value for the dead space/tidal volume ratio (V_D/V_T). Unfortunately the T_LCO obtained in this way is very sensitive to the chosen value of this ratio. This is particularly true when the V_D/V_T is normal or high and makes the method unacceptable for all but exercise studies. In fact Marie Krogh's T_LCO at rest fell threefold when the assumed dead space was changed from 140 to 100 ml!

Filley et al. (1954) directly measured the physiological V_D/V_T ratio in the conventional way, by comparing arterial PCO$_2$ with that in mixed expired gas, and then calculated the P_ACO from the Bohr equation. This requires arterial blood sampling, and assumes that its PCO$_2$ is equal to the mean alveolar PCO$_2$, which cannot be the case in patients with a significant dispersion of $\dot{V}_A/\dot{Q}$ ratios. This method is also sensitive to error. Filley himself pointed out that modest inaccuracies in expired PCO (2%) and P_aCO$_2$ (5%) could alter T_LCO by as much as 40%. Despite these disadvantages the technique has been used successfully on a variety of patients, particularly those who find special breathing manoeuvres difficult or during exercise.

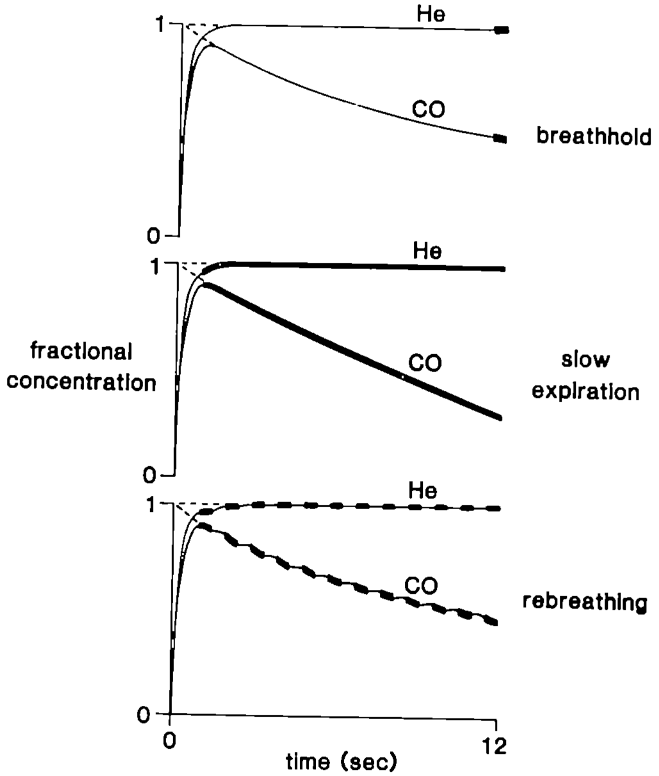


Fig. 3. How the alveolar concentrations of helium and carbon monoxide (as a fraction of the maximum helium concentration) change during the three non-steady state manoeuvres described in the text. The dotted lines show the extrapolations needed for the calculation of T_L and the thickened lines indicate the data that is actually collected. Note the relative abundance of information in the lower two panels compared with that provided by the breathholding method

A year later Bates et al. (1955) directly sampled end-tidal gas to estimate mean alveolar $P\mathrm{CO}$. As with Filley's method this will be in error in patients whose lungs have an uneven distribution of diffusing properties, as the end-tidal sample will not be representative of the whole lung and will underestimate the true $T_{L}\mathrm{CO}$.

Morphometric estimates

Weibel's group have offered a different way of studying lung diffusion, by quantitative morphology (Weibel 1973). By making careful measurements on many electron-micrographs they have obtained the mean thickness of each component of the alveolar–capillary membrane, the total alveolar surface area and capillary volume. From this data, together with estimates of the physical properties of oxygen in tissue and blood, they have calculated confidence limits for $T_{L}\mathrm{O}_2$ (Gehr et al. 1978).

These morphometric estimates are made in lungs inflated to TLC and fixed in a way that causes complete unfolding of the alveolar epithelium, and yield values that are considerably higher than measured values. Their latest lower limit for man, however, is close to the T_{L} seen on maximum exercise (up to around 33.5 mmol/min/kPa or 100 ml/min/torr).

The technique has given some particularly interesting comparative information. When T_{L} is set alongside maximum oxygen consumption large animals tend to have a relatively higher T_{L} than small animals (Gehr et al. 1981). Equation (1) shows that this implies a smaller alveolar-capillary $P\mathrm{O}_2$ gradient. If the mean alveolar $P\mathrm{O}_2$ was less in large animals (perhaps because of a longer diffusion pathway between the inspired gas front and the alveolar wall), then it is even possible that a morphological adaptation has occurred in the lung so as to increase T_{L}. This has been demonstrated in animals whose oxygen consumption has been forced to increase, or who are raised under hypoxic conditions (Weibel & Gil 1977).

Table I. The mean of $T_{L}\mathrm{CO}$ (±SD) in mmol/min/kPa (ml/min/torr) by the three common methods of measurement, in normal subjects at rest and on exercise

Method	$T_{L}\mathrm{CO}$ *at rest*	*n*	$T_{L}\mathrm{CO}$ *on exercise*	*n*
Single-breath (breathhold)	11.4±2.7 (34±8)	45	15.8±2.3 (47± 7)	12
Rebreathing	9.7±1.3 (29±4)	8	15.4 (46)	4
Steady-state	7.0±1.3 (21±4)	34	13.4±4.4 (40±13)	27

Compiled from the results of many authors by Piiper and Scheid (1980). *n* is the number of papers consulted in each case.

WHY DIFFERENT METHODS MAY GIVE DIFFERENT RESULTS

The breathholding method of measuring $T_{L}\mathrm{CO}$ is the most frequently reported, but there are also many results in the literature obtained during rebreathing and by the steady-state technique. The values in normal subjects obtained during rest and mild exercise, taken from a review of many papers compiled by Piiper and Scheid (1980), are summarized in Table I.

Why should these figures be different and how will disease affect these differences? It is well-known that the determinants of gas exchange in the lungs are unevenly distributed, mainly due to the influence of gravity. Blood flows show the greatest vertical gradient, but the transfer factor and ventilation also show substantial variations. In disease these inhomogeneities may be dramatic. Yet these three estimates of $T_{L}CO$ are calculated on the premise that the lung is entirely homogeneous—a single-compartment lung. This clearly false assumption has to be made to arrive at a concise and useful description of the diffusing properties.

So in real lungs true $T_{L}CO$ and the measured value will differ and the extent of this discrepancy will depend on the method used. The breathhold was originally thought to be relatively independent of inhomogeneities as the helium and carbon monoxide would be distributed similarly on inspiration. However, the disappearance of carbon monoxide during the breathhold depends on the ratio of T_L to alveolar volume. An uneven spread of this ratio throughout the lung will lead to a non-monoexponential decrease of carbon monoxide and so a reduction in calculated T_L which will be more striking with longer breathholding times. Uneven ventilation/volume ratios in the lung will also underestimate T_L, but only in as much as lung volume itself is underestimated by the helium dilution.

By contrast the rebreathing technique has the virtue of mixing up the gas from all lung regions and should come close to abolishing the dependence of apparent T_L on functional inhomogeneity. The lower value for rebreathing compared with single-breath $T_{L}CO$ seen in Table I is largely because the former measurement is made at a lower lung volume. When the two are compared at the same lung volume the rebreathing estimate is some 30% greater (Adaro et al. 1976). This high value is largely due to the much more homogeneous lung, although the associated hypoxia and hypercapnia cause a more rapid combination of carbon monoxide with haemoglobin and will also tend to raise $T_{L}CO$.

The steady-state measurement is made during normal breathing, but seems most affected by inhomogeneities. The functional inequalities may truly be greater in such a subject than in one who has inspired right up to TLC. This would be especially true of a patient below his closing volume. In addition variations in the ratio of T_L to alveolar ventilation will reduce measured $T_{L}CO$. Filley's method uses arterial $P\text{CO}_2$ to calculate alveolar $P\text{CO}$, and since alveolar $P\text{CO}_2$ is much more affected than $P\text{CO}$ by the best-documented inhomogeneity (that of $\dot{V}_A/\dot{Q}$), there will be further errors in T_L. Paradoxically in this particular case true T_L will be overestimated.

Variations in blood flow ($\dot{Q}$), however, throughout the lung should normally have little effect on apparent T_L, as the uptake of carbon monoxide is virtually independent of $\dot{Q}$ (except as far as $\dot{Q}$ can affect the volume of blood in pulmonary capillaries). If $\dot{Q}$ is very low then some perfusion limitation of uptake may be detectable and so some dependence of T_L on $T_L/\dot{Q}$ distributions. This is true of all methods.

On mild exercise $T_{L}CO$ rises (Table I) as pulmonary capillaries are distended and previously empty ones are recruited. On severe exercise this can raise the area of contact between gas and blood enough to triple $T_{L}CO$. As the functional inhomogeneity throughout the lung is reduced the three methods show much closer agreement.

So which method represents the 'best buy'? Most have settled for the reproducibility and standardization of technique available from modern single-breath apparatus. It is generally acceptable to patients, can be used for larger-scale screening studies and yields helium dilution lung volume as well as T_LCO. The T_L is often divided by this volume to give KCO as it is accepted that T_L normally varies directly with lung volume (Rose et al. 1979), although the range over which this occurs is disputed. KCO is then thought of as an index which compensates for the differing lung volumes of different patients and which gives information about diffusion per litre of alveolar volume rather than the lung as a whole. It can be a more sensitive index of early disease.

The breathholding method is much less easy to use for more specialized studies—during exercise, sleep or anaesthesia, or in very breathless patients. In these instances the steady-state technique is simple and can be said to be more physiological, as the other methods involve Muller and Valsalva-like manoeuvres. No helium analyser is needed. It is, however, the most sensitive to functional inhomogeneities and its errors are greatest when the T_L is low and the dead space is high. This is the case in many of the instances cited above and so rebreathing may become the method of choice. This is especially true for the severely ill and it gives the T_LCO nearest to the true value summed throughout the lung.

WHAT IS REALLY MEASURED?

The discussion above has explained how the various methods of measurement of T_L are affected by the inequalities present in both normal and diseased lungs and so will not necessarily sample the 'same' lung in any one patient. Neither will any particular method measure precisely the same facet of lung function in different diseases. For this reason it is difficult to give an unguarded answer to the question 'what does T_LCO really measure?'

The T_LCO has evolved from being regarded as a measure of membrane properties, to one in which the properties of capillary haemoglobin are at least equally important. We also have a better understanding of the ways in which the distributions of gas volume. ventilation and diffusing properties may affect carbon monoxide uptake. In a single unit one can say that T_LCO measures the barrier to gas exchange presented by the alveolar–capillary membrane and diffusion towards and subsequent chemical combination with, haemoglobin. In the whole lung one has to be more general and say that T_LCO represents the access that inspired gas has to the pulmonary capillary haemoglobin in the particular breathing manoeuvre used.

PHYSIOLOGICAL VARIATIONS IN T_LCO

Despite such limitations on our ability to interpret T_LCO precisely, it has a firm place in any assessment of lung function and it is important to establish normal limits. The regression relationships for the prediction of T_LCO, D_M, V_c and KCO from age, sex and height in Cotes (1980) are widely used in the UK and values within 10–20% of the predicted taken to be normal. They show that T_LCO increases throughout childhood but not as fast as lung volume, leading to a drop in KCO. In adult life both T_LCO and KCO decrease with age, with drops in both D_M and V_c (Georges et al. 1978). Any differences between the sexes or with physical activity are accounted for entirely by the associated difference in lung volumes. Such relationships derived from subjects of European descent cannot, of course, necessarily be applied to others, although little differences in T_LCO have been described between races.

Pulmonary capillary blood volume, and so T_LCO will decrease on standing up, on IPPV, after taking alcohol or a meal or with any other cause of blood shifting to the periphery. This should be taken into account when testing patients. Conversely increases in V_c, such as occur on lying down or immersion in water, will raise T_LCO.

As mentioned earlier, the derivation of Kco as the ratio of T_LCO to alveolar volume is a useful correction of T_L for lung sizes that vary, whether due to disease or to different body sizes. Another useful correction that should be applied to T_LCO is for haemoglobin concentration, as the T_L will rise in polycythaemia and fall in anaemia simply due to more or less haemoglobin being available in the pulmonary capillary. Observed T_L is adjusted in accord with equation (2), since θ refers to the reaction rate of carbon monoxide with 1 ml of blood with a standard haemoglobin level of 14.6 g/dl. Details of this correction are given by Cotes (1980).

An interesting situation occurs at high altitude (West 1962) where lowlanders show only a small increase in T_LCO (15–20%), exercising at 5800 m. Even this is wholly accounted for by the increased reaction rate due to hypoxia and polycythaemia, although recent evidence in dogs suggests that capillary recruitment may also play a part in the response to more acute hypoxia (Capen et al. 1981). By contrast natives to high altitudes show a substantial rise in T_LCO and this is a particularly appropriate adaptation to their environment.

A small fraction of haemoglobin in the blood of non-smokers is normally present as carboxyhaemoglobin (COHb) due to pigment breakdown and to any air pollution with partially burnt hydrocarbons. The upper limit of this amount is 2.5%. The concentration of carbon monoxide in cigarette smoke is up to about 4%, approaching that in car exhausts! This raises the COHb fraction to 5–10% or even higher, the sort of level that has been shown to impair CNS function.

Since the dissociation of carbon monoxide from COHb is slow (half-time of over four hours) allowance must be made for this back-pressure when measuring T_LCO in a smoker. Failure to do so will result in an underestimate of up to 20%. This is best done by direct determination of mixed venous *P*CO by a rebreathing procedure.

Even when this correction is made, smokers have a T_LCO and Kco some 10–20% lower than non-smokers of the same age. This is more marked in females. The T_LCO of smokers also drops more rapidly with age. In fact measurement of Kco has been presented as the best of a range of lung function tests to distinguish smokers from non-smokers (Becklake & Permutt 1979). The reason for the drop in T_LCO is uncertain. Most studies favour a drop in pulmonary capillary blood volume, but some reduction in D_M has also been observed.

FINDINGS IN DISEASE

T_LCO is often thought of as giving information about the blood–gas barrier, but the situation is complex. In disease, inhomogeneities throughout the lung make it difficult to infer the properties of the barrier from such a measurement. Equally although inhomogeneities generally reduce the measured T_L, some patients with marked unevenness of ventilation (e.g. asthma or type B COPD) typically have a well-preserved T_LCO. Such cautions certainly do not negate the role of T_LCO in the assessment of abnormal lung function, although it often has to be used somewhat empirically. Table II gives the functional headings under which disturbances of T_L can be listed. Some of these will be considered here, and it will be assumed that the single-breath (breathhold) method has been used unless stated otherwise.

Table II. The factors which influence T_{L}CO

Membrane	*Blood*	*Inhomogeneities*
Surface area destruction alveolar filling	Capillary volume	Ventilation to volume ($\dot{V}_A/V_A$)
Thickness	Haemoglobin concentration	Transfer factor to volume (T_L/V_A)
	Intra-alveolar haemoglobin	

Membrane

A reduction in the area of membrane available for diffusion is an important cause of a low T_LCO. It is seen for example after the alveolar wall destruction of emphysema and bullous conditions or after the alveolar filling that occurs in pulmonary oedema, pneumonia or granulomatous diseases. The most striking reduction is in patients with emphysema and the steady-state technique gives even lower values because of the inhomogeneities that are so prominent in this disease. In type B COPD the T_LCO is unaffected and a low value is a sensitive indicator of the coexistence of emphysema. Kco may be superior as the helium dilution volume is better preserved than the T_LCO.

The surgical destruction of membrane area that occurs after lung resection will naturally reduce T_LCO. Interestingly this subsequently improves more than the lung volume leading to a rise in Kco. The relative increase in blood flow through the remaining lung may cause a higher capillary volume, although no such compensatory change seems to occur in children.

One of the fingerprints of interstitial lung disease of various aetiologies is a low T_LCO and Kco, especially the membrane component, although the mechanism of this reduction is still uncertain. Curiously, the degree of reduction may not correlate with the histological severity of the disease (Fulmer et al. 1979). Careful morphometry has shown that the thickening of the alveolar–capillary membrane seems relatively mild compared with the loss of its surface area. The membrane is seldom even twice its normal thickness (Divertie et al. 1976) The relative importance of the reduction in V_c is uncertain. Whatever the mechanism of the low T_LCO, it is the most severely impaired aspect of lung function that is usually measured, and particularly in early sarcoidosis may be the only such abnormality. Diseases causing restriction of the chest wall as opposed to the lungs do not alter T_LCO.

Blood

Many diseases cause a low capillary blood volume. Most conspicuous are primary pulmonary hypertension and recurrent pulmonary embolism. Indeed the fall in capillary volume is often more striking than the rise in pulmonary arterial pressure and so the measurement of T_LCO has been put forward as a sensitive index of such vascular obstruction. Large acute embolism has a much less marked effect on T_LCO. It is uncertain how much any unevenness of diffusing properties throughout the lung contributes in these vascular diseases.

If the blood next to the alveolar gas is very slowly flowing or static, as after a pulmonary embolus, then a back-pressure of carbon monoxide will rapidly build up. This causes successive estimates of T_{L}CO to decrease. Such a phenomenon has been exploited to demonstrate pulmonary vascular obstruction (Hallenborg et al. 1969). Haemorrhage into the alveoli from any cause may increase Kco and its measurement is a useful way of following progress in such patients (Lipscomb et al. 1978).

Any change of T_{L}CO in mitral stenosis can conveniently be explained by a combination of mechanisms. On the one hand the increased left atrial pressure raises V_{c}, but on the other hand any pulmonary oedema will reduce D_{M}. Later in the disease pulmonary vascular obliteration will reduce V_{c} too, which prevents the rise in T_{L}CO that normally occurs on exercise. The increased pulmonary blood flow seen in intracardiac left-to-right shunts may increase V_{c} considerably, due mainly to recruitment of vessels in the upper parts of the lungs. The high T_{L}CO in these cases is reversed by surgical correction of the heart defect.

The well-preserved T_{L}CO of asthmatics was mentioned earlier. In fact it (and especially the Kco) can even be high. This is attributed to a more even distribution of blood flow causing recruitment of new capillaries. The latter could be due to a reduced intrathoracic pressure caused by inspiratory obstruction and can be mimicked in normal subjects (Keens et al. 1979). In any event the alveolar–capillary membrane is unaffected and (as in type B CPOD) a normal T_{L}CO is useful in excluding significant emphysema. Drug-induced bronchospasm causes a greater drop in T_{L}CO than occurs during an acute attack of asthma, when the T_{L} is often normal.

HOW DOES THE T_{L}CO RELATE TO OXYGEN TRANSPORT IN THE LUNG?

When carbon monoxide is used to measure T_{L} its very high 'solubility' in blood means that gas–blood equilibrium is not even approached and that the A–aPco gradient (in relation to the alveolar Pco) is huge. Indeed it is just that property of carbon monoxide that allows it to measure the potential barrier to the transfer of gas between alveolar air and blood. For oxygen and carbon dioxide the barrier is not as great. This is because they are much less soluble in blood and so less need be transferred in order to reach gas–blood equilibrium. The time courses of the partial pressures of these two gases as they approach this equilibrium in the pulmonary capillary is similar and that for oxygen is illustrated by the upper curve in Fig. 4.

It can be seen that the blood $P\mathrm{o}_2$ has risen to that in alveolar gas by the time the red cell has passed one-third of the way along the capillary. Thus the uptake of oxygen has a three-fold reserve. If the membrane diffusing capacity (D_{M}) is reduced five-fold, as in the lower curve, then equilibrium is certainly incomplete, and a substantial A–a$P\mathrm{o}_2$ gradient appears (Wagner & West 1972). This is referred to as diffusion impairment of oxygen transfer. Note that this implies a much greater disability than does a reduced T_{L}CO.

Thus on the one hand T_{L}CO is a sensitive index of the lungs' reserves of ability to transfer gas between alveolar air and blood. On the other hand a reduced T_{L}CO does not answer the common question as to whether, in any particular patient, diffusion impairment is playing a part in his hypoxaemia. In diseased lungs disturbances of ventilation/perfusion relationships are usually the major cause of hypoxaemia and make any diffusion component all the more difficult to distinguish. Yet the treatment of these two defects may be quite different. Theoretically diffusion impairment for oxygen should be the more apparent if alveolar Po_2 is low (there is less alveolar–capillary head of pressure and the effective 'solubility' of oxygen is higher on the steep part of its dissociation curve), and when the time spent in the pulmonary capillary is reduced. There is evidence that normal subjects exercising at high altitude show an A–aPo_2 gradient for these reasons.

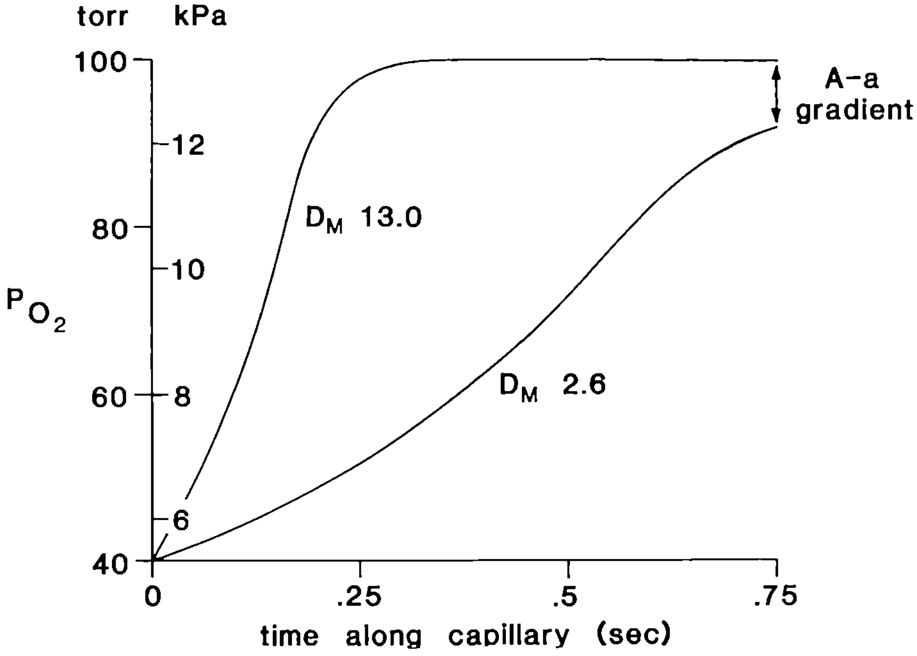


Fig. 4. The calculated rise of red cell Po_2 as it passes through the 'typical' pulmonary capillary, plotted against time. The upper curve is for a normal membrane diffusing capacity (D_M), whereas the slower rise of the lower curve is due to a five-fold reduction in D_M. In both cases Po_2 starts at the mixed venous value (5.3 kPa or 40 torr) and approaches the alveolar level (13.3 kPa or 100 torr). Note the failure to equilibrate, or appearance of a sizeable A–aPo_2 gradient, in the lower curve

In disease it is possible that these conditions exist in a substantial portion of the lungs. The alveolar Po_2 will certainly be low in a region with a low ventilation/perfusion ratio and if the capillary architecture is distorted the transit time may also be shortened. However, calculations have suggested that the shape of the oxygen dissociation curve conveys a rather remarkable protection against diffusion impairment (Wagner & West 1972). The A–a gradient produced by a given degree of membrane abnormality is least in lung regions with abnormal ventilation/perfusion ratios (low *or* high). Thus the areas that are the most diseased may have the best ability to cope with potential diffusion barriers.

This is speculation, however. In practice it is possible to measure the distribution of ventilation/perfusion ratios in diseased lungs and so (by exclusion) to estimate the amount that diffusion impairment is contributing to any hypoxaemia. This technique of multiple inert gas elimination (Wagner & West 1980) is rather complex but probably gives the best answer to this question.

Many such studies have only detected one circumstance under which diffusion impairment may play a significant role in the hypoxaemia of lung disease. In patients with advanced interstitial lung disease who are exercising, some 15% of the A–aP_{O_2} gradient has been attributed to a diffusion barrier. None the less $T_{L}CO$ remains a sensitive index of abnormalities in the path between alveolar gas and haemoglobin, even if its use in most diseases is based on a still too poor understanding of the pathophysiology.

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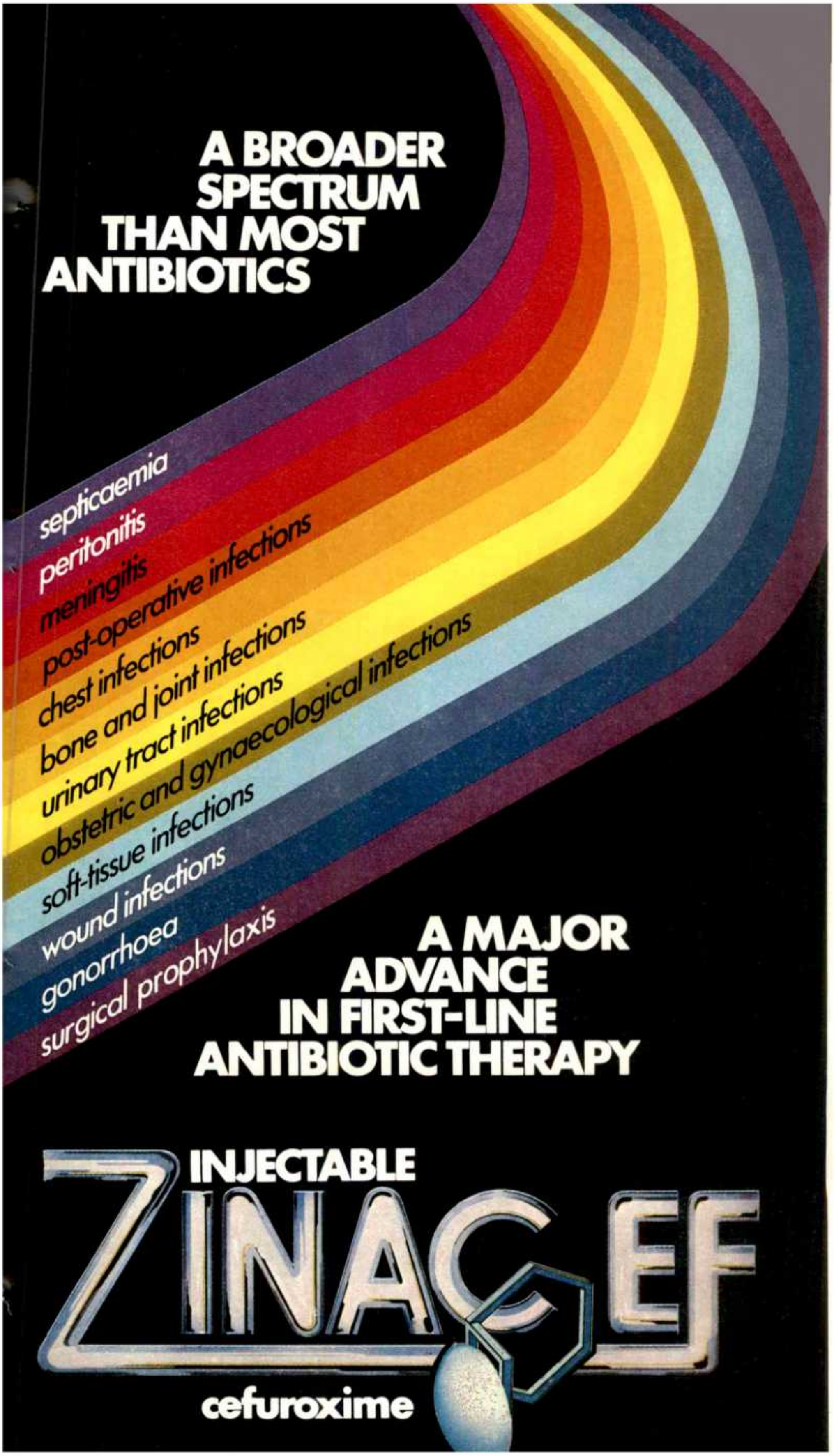

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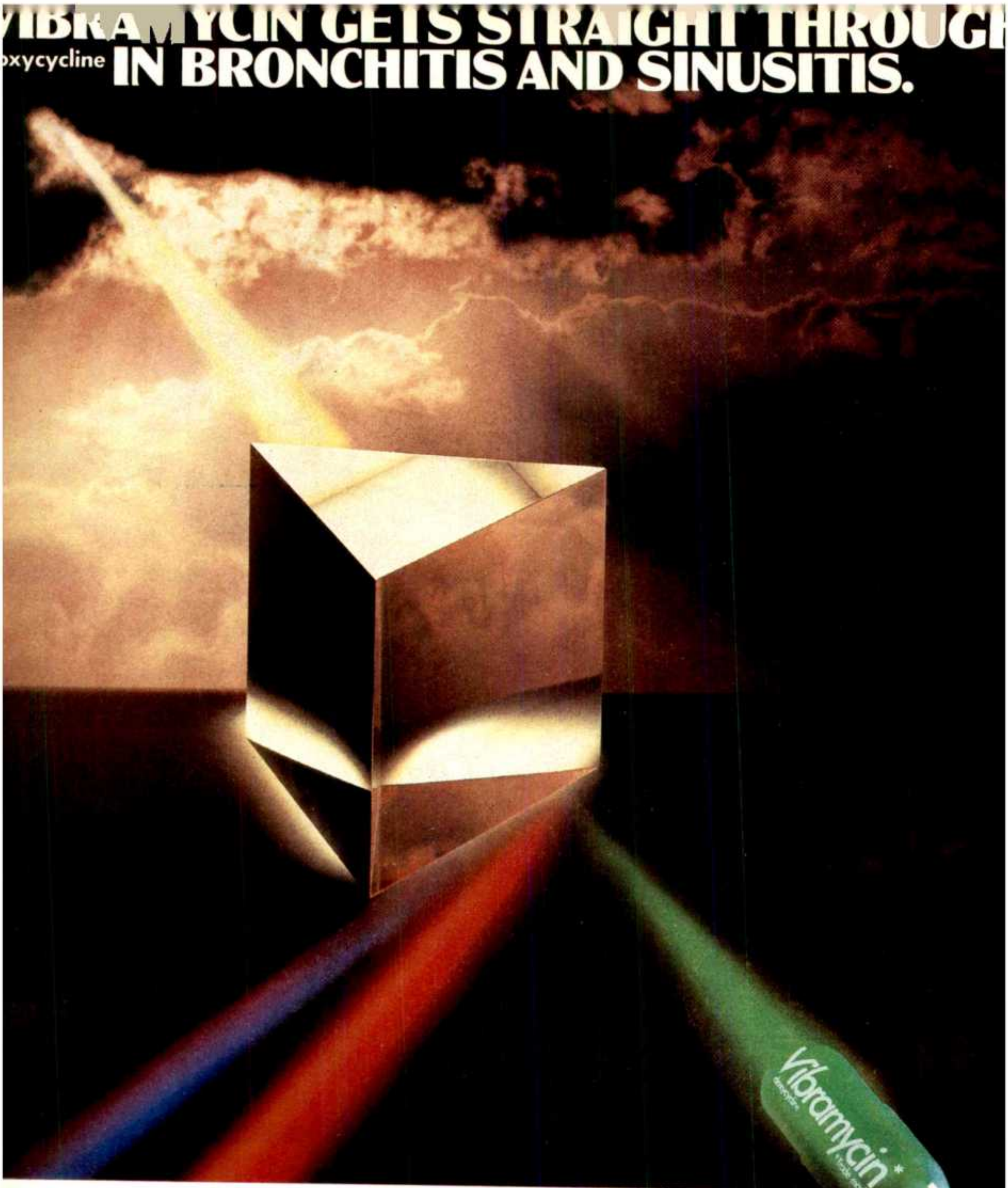

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Br. J. Dis. Chest (1982) *76*, 125

Controversy

ARE CORTICOSTEROIDS NECESSARY IN THE TREATMENT OF SEVERE ACUTE ASTHMA?*

IAN W. B. GRANT

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In clinical medicine, perhaps more than in any other area of scientific endeavour, we are prone to become prisoners of our traditional preconceptions. Gradually in most cases, but rapidly in a few, many of these preconceptions have been swept away. It took centuries for bed rest in the treatment of many serious diseases, such as pulmonary tuberculosis and coronary thrombosis, to be discredited, and decades for the barbarous practice of removing healthy tonsils from healthy children to be abandoned. In contrast, the discovery that high-concentration oxygen therapy in patients with ventilatory failure could cause coma and death had an immediate impact. In some of these instances, and in many others, therapeutic policy has turned full circle and forms of treatment once considered logical and beneficial have come to be regarded as irrational or even positively harmful.

The iconoclast in medicine, although not always a popular figure in the profession, has often helped to open the way to major therapeutic advances. Yet it is important to realize that there can be false iconoclasts as well as false icons and that in their separate ways both can be dangerous. George Bernard Shaw, although not a doctor, was a powerful opponent of vaccination against smallpox, asserting in his well-publicized ignorance that the decline in the incidence of that disease was the result not of vaccination but of improved sanitation. He has now been proved completely wrong, but one of my most painful personal recollections is that of witnessing the death of an intelligent and well-read young soldier from haemorrhagic smallpox in India during the War after he had refused vaccination in the belief that the opinion of a man with the intellect of Shaw was more to be trusted than that of a Regimental Medical Officer. Although that is, of course, a bizarre example of the damage which can stem from a misinformed iconoclastic approach, it epitomizes the grave responsibility which doctors must accept when they publicize views which are diametrically opposed to those of the majority of their colleagues. No such crisis of conscience arises when a doctor, even perhaps quite wrongly, deems dangerous a drug which has been used uncritically for many years, but for which there is an adequate substitute. It is a different matter, however, to condemn a form of treatment which in certain circumstances *may* be life-saving, but, even if it is not, can do no harm if administered for short periods.

The views expressed in Dr Luksza's two articles, questioning the value of corticosteroids in the treatment of severe acute asthma, come into the second category. In purely scientific terms there is a lot to be said in his support. It has never been proved by a controlled clinical trial that corticosteroids in this condition actually save lives, and

* The Editor has invited Dr Grant to write this paper as a comment on the two papers by Dr A. Luksza which were published in our January 1982 issue.

strictly speaking it is irrational to prescribe any form of treatment when there is no objective evidence that it alters the course of the disease for which it is given. On the other hand, few respiratory physicians would agree with Dr Luksza's statement that 'far from preventing asthma deaths, steroids may well have contributed to them', a hypothesis for which he presents only the flimsiest circumstantial evidence. Many studies (Cochrane & Clark 1975; MacDonald et al. 1976*a*, *b*; Hetzel et al. 1977; Cooke et al. 1979; Ormerod & Stableforth 1980) have on the contrary suggested that *under-use* of corticosteroids is an important factor associated with deaths from asthma and shown that in a surprisingly large number of fatal cases the patient has not received systemic corticosteroid therapy in any form.

If, therefore, Dr Luksza seriously believes that corticosteroids in severe acute asthma are unnecessary and perhaps even dangerous, the onus is on him to provide convincing proof of these contentions. However philosophically satisfying he may find it to withhold corticosteroids in that situation, he is bound to expose himself to the charge that his policy may put at risk the lives of at least some asthmatic patients and result in others being unnecessarily intubated and ventilated.

Looking first at his article on 'Acute severe asthma treated without steroids', the most immediately disquieting feature is the high proportion of patients (13 of 90) in whom tracheal intubation and mechanical ventilation (IPPV) was required. That procedure had to be instituted in 10 (21%) of the 48 patients who had not been taking corticosteroids before admission to hospital, but in only three (7%) of the 42 who had. Although this difference does not quite reach statistical significance at the 5% level, it raises the question as to whether at least some of the 10 patients who had not been given corticosteroids (even prednisolone by mouth) before admission might not have required IPPV if they had been so treated.

Dr Luksza makes the point that in four patients not treated with corticosteroids IPPV was started within two hours of admission, and that it probably could not have been averted by treatment with hydrocortisone. Admittedly, severe acute asthma can develop very rapidly, but few such patients are *in extremis* less than two hours after the onset of an attack and Dr Luksza can hardly deny that if corticosteroids had been given at an earlier stage to these patients (by their general practitioners), not all of them might have required IPPV. Moreover, it is hardly to the credit of whoever was supervising the 48 patients who were not previously being treated with corticosteroids that so large a number should have developed asthma of such severity that they had to be admitted to an intensive care unit. Experience in Edinburgh (Crompton & Grant 1975) has shown that it is usually possible to identify patients who are liable to develop life-threatening attacks of asthma. The treatment of all such patients, unless their asthma is of the relatively uncommon corticosteroid-resistant type (Carmichael et al. 1981), invariably includes a maintenance dose of oral prednisolone. In addition, they are accorded facilities for immediate self-admission to hospital in the event of their developing an acute attack. The outcome of this policy is that in Edinburgh IPPV is now required in less than 2% of admissions (Cooke et al. 1979), as compared with 14% in the Liverpool series. Because there is no mention of arterial blood gas studies in Dr Luksza's article, it is impossible to determine whether the two series were comparable in terms of the severity of asthma. If they were, the less frequent resort to major resuscitative measures in Edinburgh may have been related to the more prompt and liberal use of corticosteroids in severe asthma, facilitated in many cases by the operation of an efficient self-admission system (Crompton et al. 1979).

These observations do not, *ipso facto*, refute Dr Luksza's claim that corticosteroids may be unnecessary or even potentially dangerous in the treatment, as distinct from the prevention, of acute attacks of asthma. In order to do so a prospective randomized controlled trial, comparing an active corticosteroid preparation and a placebo, would be required, and most respiratory physicians would consider such a trial unethical. Nobody would deny that patients can survive a very severe attack of asthma without being given corticosteroids, but some of Dr Luksza's patients in that category might well have died if expert facilities for IPPV had not been available. In other circumstances corticosteroids might not have kept these patients alive, but the crux of the argument is that whereas the withholding of that form of treatment *may* contribute to a fatal outcome, the administration of corticosteroids, certainly in short courses, *never* kills patients with severe acute asthma. Dr Luksza in effect challenges the second part of this statement by claiming that immunosuppression caused by corticosteroid therapy (presumably he means long-term treatment) may be an important contributory factor in deaths from asthma, but his evidence for this contention rests solely on the deaths of two patients from overwhelming sepsis, one in his own study and the other in the original controlled trial carried out by the Medical Research Council (1956). Two deaths in 25 years amongst thousands, or even tens of thousands, of cases of severe acute asthma treated with corticosteroids is hardly a sound basis for any claim that this form of treatment is dangerous.

In short, Dr Luksza's study has failed to provide any convincing evidence that corticosteroids can properly be withheld in the treatment of patients with severe acute asthma.

Dr Luksza's second paper, entitled 'A new look at adult asthma', seeks to justify his prejudice against the value of corticosteroids in severe acute asthma. His arguments are extremely difficult to understand. For example, he claims that 'severe acute asthma' and 'gradually deteriorating airway obstruction' are distinct clinical entities, but later proceeds to state that 'severe acute asthma develops rapidly either from a background of normal respiratory function in labile asthma or, more commonly, from a prolonged period of gradually deteriorating airway obstruction'. He then postulates that 'steroids may prevent the onset of severe acute asthma by treating gradually deteriorating airway obstruction, but they are ineffective once severe acute asthma is established'. The corollary to this is that corticosteroids should be reduced to a physiological level of dosage whenever gradually deteriorating airway obstruction advances to the stage at which it merits the description of 'severe acute asthma' because at that stage, according to Dr Luksza, they enhance the cardiotoxicity of β-adrenoreceptor agonist drugs and may cause death. Patients with severe acute asthma of sudden onset are said to die as a result of 'circulatory effects' (whatever that may mean), while these are less important in patients who die from less rapidly progressive severe asthma. In fact, the cause of death in all patients with acute asthma is hypoxic cardiac arrest. Thus, the suggestion that because this takes longer to supervene in some asthmatics than in others, therapeutic policy should be geared to the tempo of deterioration and not to the actual severity of the airway obstruction is manifestly absurd.

Dr Luksa next poses the question that 'if steroids are beneficial in severe acute asthma, why then does not endogenous cortisol act therapeutically in this situation?'. The obvious answer is that even in very severe asthma, previously untreated with corticosteroids, endogenous plasma cortisol concentrations are far below those produced by the massive pharmacological doses of exogenous corticosteroid usually prescribed in such cases and that in some they are only slightly increased (Collins et al. 1970).

Then follow the observations (*a*) that asthma deaths have not decreased significantly since the introduction of corticosteroids and (*b*) that corticosteroid therapy, if effective, should have averted deaths by preventing severe acute attacks of asthma. These observations, and the conclusions Dr Luksza draws from them, can be relevant only if it is assumed that the vast majority of patients who develop severe acute asthma are given corticosteroids in appropriate dosage and that this treatment is started very shortly after airway obstruction ceases to respond to conventional treatment with bronchodilator drugs. That this assumption is false is clear from one important published report (Speizer et al. 1968), and indeed from Dr Luksza's own paper on 'Acute severe asthma treated without steroids', since no less than 48 of the 90 patients who required admission to his intensive care unit had not been given corticosteroids. It is thus totally incomprehensible that he should proceed to claim that any increase in case fatality rate (of which he provides no factual evidence) may be related to 'inappropriate use of steroids'.

In his first paper Dr Luksza evokes the spectre of immunosuppression and fulminating infection (two cases!) to discourage the use of corticosteroids in severe acute asthma, but he has conjured up a new spectre in his second paper: the possibility that 'sublethal doses of isoprenaline in the presence of hypoxaemia and systemic steroid therapy' may have been responsible for the 'epidemic' of asthma deaths in the mid-1960s. He has obviously forgotten that when the number of deaths began to fall at the end of this 'epidemic' there was a dramatic *increase* in the prescription of oral corticosteroids and it is now generally believed that this, together with prompt admission to hospital, was a more important factor in reducing asthma mortality than restrictions in the use of isoprenaline inhalers.

Dr Luksza's final sweeping conclusion that 'far from preventing asthma deaths steroids may well have contributed to them' is interesting and challenging, but the evidence he cites in support of it is insubstantial and in many respects spurious. He has certainly shown that patients under his personal care with severe acute asthma can survive without systemic corticosteroid therapy, but does he know how many patients in other circumstances have died, or may die in the future, if that form of treatment is deliberately withheld? Until we have an answer to that question his views must be regarded with the utmost reserve.

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Br. J. Dis. Chest (1982) *76*, 130

THE USE OF A MICRO-COMPUTER SYSTEM IN A LUNG FUNCTION TESTING LABORATORY

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Summary

This report describes the use of a relatively inexpensive micro-computer, floppy disk drive and printer, now costing about £2000, in a routine lung function testing laboratory in a district general hospital. The computer calculates and types the results of lung function tests and calculates normal values and percentages. In addition it automatically generates a typed commentary on the results, files the current results on the disk and searches and tabulates previous results. The computer can produce lists of patients with particular characteristics and can also be used for other purposes.

INTRODUCTION

Except for highly specialized functions, computer technology has been surprisingly slow to gain acceptance in clinical areas of hospital medical practice. Most hospitals possess or have access to some form of computing facility, but the ineffective use of large computers, and the delays and mistakes that appear to be inherent in many computerized systems, have added to the disillusionment many clinicians feel about the possibilities for use in their own practice. Small electronic processors are now built into many monitoring or pulmonary physiological measurement systems, but these often seem to add but a small advantage to the testing and a large amount to the capital cost. In some ways an individual unit or laboratory resembles a small business. Many small commercial concerns and offices are discovering the advantages of small computers and these are also applicable to many hospital departments. We purchased a Commodore 32K micro-computer (costs now about £600), a Computhink 800K dual floppy disk drive (costs about £900) and a Commodore 3022 printer (costs about £425) for use in a routine lung function laboratory. I describe the use of this system for calculating, reporting, typing and filing the results of lung function tests.

WHY BOTHER WITH A COMPUTER?

There have been several accounts of the use of computers in a lung function laboratory. Schonfield et al. (1964) described the analysis and reporting of spirograms by a remote computer and Hoffer et al. (1973) described computer analysis of ventilatory studies using a terminal communicating with a remote computer. Pack et al. (1977) recorded the Glasgow experience and noted the frustration and lack of job satisfaction for technicians when using a large computer shared with others and with results entered and processed in batches two or three times a day. Geddes et al. (1978) recorded the experience at Westminster Hospital where results were obtained from a distant computer through a video terminal, but were then copied down by technicians, with consequent increase in clerical errors. A small desk-top machine was used by Chiang (1972) to calculate results, generate a report and operate a simple output printer using pre-printed forms. Ellis et al. (1975) used a more sophisticated programmable calculator with a keyboard, cathode ray tube, electric typewriter and magnetic tape cassette recorder with satisfactory results.

Modern apparatus is more compact, more simple and more versatile and has a relatively large storage capacity. It is also cheaper and with a total cost of less than £2000 is within the scope of all but the smallest lung function laboratories.

Our requirements from a computer system were simple but comprehensive:

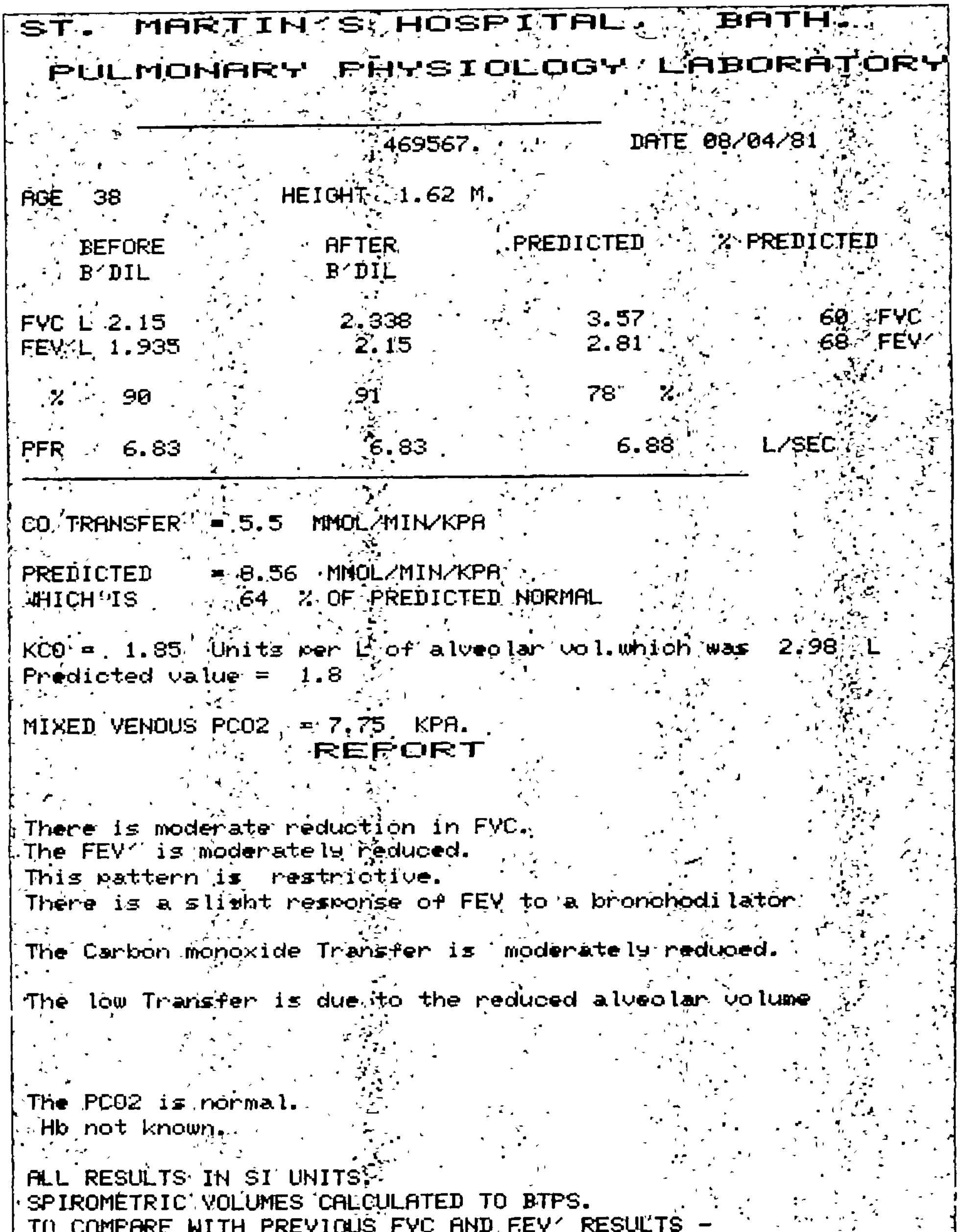
1. It should be easy to use.
2. It should be adaptable, if necessary by the user.
3. It should require the minimum of keyboard entry work (technicians are not trained typists).
4. The computer should generate the predicted normal values from standard formulae.
5. The computer should apply correction values (traditional to SI units, BTPS corrections, allowance for haemoglobin) where appropriate.
6. The computer should generate a commentary ('report') on the results.
7. The printer should produce two copies of the final results and report.
8. The results should be filed automatically within the computer system.
9. Previous results should be checked automatically and tabulated at the end of each printed report.
10. The filed results should be available for a variety of purposes.

Several machines are suitable for this purpose, but the one we chose was particularly attractive because of the large storage capacity of each disk. Our system fulfils all the above requirements and the reports are typed much more quickly than could be done by even a skilled typist. (The output of the printer is 80 characters or one line of text per second.) It is possible to file the results of tests on 2500 patients on each disk, should this large number be desired.

How the Micro-computer is Used

We did not think it desirable for the computer to be linked directly with any measuring apparatus. Our routine lung function tests consist of measurements of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), peak flow rate (PEF), all before and after a bronchodilator; single breath carbon monoxide transfer (TLco and Kco) and mixed venous carbon dioxide tension ($P\text{CO}_2$). Static lung volumes, arterial blood gases and exercise tests are performed occasionally, but not routinely, and are not incorporated in the computer program although there is ample space for all these tests and many others if our policy is changed. The calculation of the TLco and Kco are performed and all results are entered in the day book as part of the routine laboratory procedure.

The current floppy disk is inserted in the disk drive and loaded into the computer by typing $L, 1, 'TESTS' on to the keyboard. The program is started by typing 'RUN'.



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ST. MARTIN'S HOSPITAL.  BATH.
 PULMONARY PHYSIOLOGY LABORATORY

                     469567.          DATE 08/04/81

AGE  38          HEIGHT  1.62 M.

    BEFORE           AFTER          PREDICTED    % PREDICTED
    B'DIL            B'DIL

FVC L 2.15           2.338           3.57              60 FVC
FEV'L 1.935          2.15            2.81              68 FEV'

 %    90             91              78   %

PFR   6.83           6.83              6.88     L/SEC

CO TRANSFER  = 5.5  MMOL/MIN/KPA

PREDICTED     = 8.56 MMOL/MIN/KPA
WHICH IS        64  % OF PREDICTED NORMAL

KCO = 1.85 Units per L of alveolar vol.which was  2.98 L
Predicted value =  1.8

MIXED VENOUS PCO2  = 7.75  KPA.
                   REPORT

There is moderate reduction in FVC.
The FEV' is moderately reduced.
This pattern is  restrictive.
There is a slight response of FEV to a bronchodilator

The Carbon monoxide Transfer is  moderately reduced.

The low Transfer is due to the reduced alveolar volume



The PCO2 is normal.
 Hb not known.

ALL RESULTS IN SI UNITS.
SPIROMETRIC VOLUMES CALCULATED TO BTPS.
TO COMPARE WITH PREVIOUS FVC AND FEV' RESULTS -
ADD APPROX 10% TO PREVIOUS VALUES.
NEW VALUES FROM 1ST MARCH, 1980.PEF,CO TRANSFER AND PCO2
```

Fig. 1. Example of a printed report

The computer then checks the number of records on the disk and establishes that there is space for a new entry. The process so far takes about 10 seconds including the time for the keyboard entries. The display screen now displays:

ENTER NAME, NUMBER, DATE?

Later there are similar requests for the age, sex and height of the patients, BTPS factor and the individual results of the tests. The screen then displays the results corrected to body temperature, the predicted values, percentage predicted and the $FEV_1/FVC\%$. The PEF results are displayed after division by 60 to appear in SI units. If appropriate the TLco result is corrected according to the haemoglobin. The operator checks the results to make sure there has been no obvious error in the entries, such as a misplaced decimal, and in response to the query 'OK?' types Y (yes) or N (no). The latter response starts the entries again. With an affirmative response the computer then prints two copies of the results followed by a printed report which is a commentary on the results. The logic of this report is similar, but not identical, to that which has been published from other centres (Ellis et al. 1975; Pack et al. 1977; Geddes et al. 1978).

The validity of such reports has been confirmed by Geddes et al. (1978) and they are in current use in several hospitals.

The computer then files the name, number, date, FVC before and after a bronchodilator, FEV_1 before and after a bronchodilator, percentage predicted transfer, $P\text{CO}_2$ and percentage response to the bronchodilator.

If there are previous results the computer searches the disk, checking the name and the hospital number and appends the tabulated results below the report.

It takes approximately one minute to enter the results; the printout takes 30 seconds per copy. The search time depends on the number of records on the disk, about 23 seconds per 100 patient records.

Additional calculations can be printed on the laboratory copy of the results and the program causes a warning to be printed if the ratio of the PEF and the FEV_1 is abnormal so as to suggest upper airway obstruction.

Separate programs can produce lists of patients with particular characteristics. This has proved useful in selecting patients to participate in research projects such as trials of bronchodilators.

Floppy disks are not as fragile as they sound, but can be damaged by being creased or scratched or overheated. The current disk is copied—a process which takes three minutes—each month so that in the event of a disaster only one month's results need be re-entered. There is no reason why this disk could not be copied each week or each day if that were desired—each disk can be re-used many times.

We have no special security problems since no-one else uses the computer and the disks are stored separately.

An example of the typed report is shown in Fig. 1.

CONCLUSIONS

We have been using this system for one year. Apart from a faulty printer (repaired under guarantee) there have been no problems. The programs are written in a simple 'language' (BASIC) and can easily be modified to change the calculations or the display of the results or the report. Laboratory technicians enjoy using the computer and undoubtedly the possibility of errors in calculating percentages has been eliminated. The typed commentary has been of considerable advantage, drawing the attention of whoever finally approves the report to the abnormality of the results where appropriate. Likewise the tabulation of previous results is valuable in observing changes. We also use the computer to elicit an allergy history from patients and to produce a disease index and bed state statistics. The computer has also been useful when performing statistical analyses, the versatility speed of the printer allowing a permanent record of all steps in the calculations. We have come to regard our micro-computer as an essential and fundamental part of our laboratory equipment and wonder how we managed without it.

ACKNOWLEDGEMENTS

The responsibility for writing the program described is my own, but I am extremely grateful to Alun Davies of the Wiltshire Area Medical Physics Department for help in steering me through the early stages of learning BASIC. I am also grateful to Miss Hazel Gimblett and Mrs J. Elmes, Pulmonary Function Technicians at St Martin's Hospital, for their willing cooperation and to Miss A. Sawyer for typing the manuscript. The apparatus was purchased with a grant from the Bath Area Medical Research Trust.

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THE EFFECTS OF NEBULIZED SALBUTAMOL ON LUNG FUNCTION AND EXERCISE TOLERANCE IN PATIENTS WITH SEVERE AIRFLOW OBSTRUCTION

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Summary

The effects of 10 mg of nebulized salbutamol on lung mechanics and exercise tolerance in 10 patients with severe airflow obstruction are described. All patients were previously considered to have irreversible airflow obstruction as demonstrated by little or no improvement in expiratory flow rates either during a corticosteroid trial or after inhalation of 100 μg of isoprenaline. There was a small improvement in expiratory flow rate after nebulized salbutamol but the greatest increases were seen in slow vital capacity, inspiratory capacity, inspiratory flow rates, dynamic compliance during tidal breathing, mid-inspiratory and expiratory pulmonary resistance and exercise tolerance. The mechanism of these effects and their therapeutic significance is discussed.

INTRODUCTION

Before reaching a diagnosis of chronic irreversible airflow obstruction it is usual practice to look hard for any evidence of reversibility which may be of therapeutic benefit to the patient. The conventional approach is to try and demonstrate an improvement in expiratory flow rate by measuring the forced expiratory volume in one second (FEV_1) before and after an aerosol bronchodilator and daily peak expiratory flow rate (PEFR) during a course of high-dose corticosteroids. Patients who do not objectively improve by these measurements do, however, sometimes claim that dyspnoea is relieved after bronchodilator inhalation.

In a randomized, double-blind, cross-over study (Wilson & Connellan 1980), patients with severe airflow obstruction who had previously derived little benefit from corticosteroid or conventional bronchodilator therapy all preferred nebulized salbutamol to placebo and the majority had noted that the relief of dyspnoea and improvement in exercise tolerance was greater after nebulized bronchodilator than after conventional pressure-packed aerosol therapy.

The aim of this study was to assess the changes in lung mechanics and exercise tolerance after nebulized salbutamol in patients considered to have severe irreversible airflow obstruction and to see if there were any objective measurements which could be useful in identifying those who might benefit from this therapy.

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Materials and Methods

Ten patients were recruited from in-patient and out-patient departments. There were nine males and one female with a mean age of 63 years and a range of 55–70 years. All had severe airflow obstruction confirmed by a decrease in $FEV_1/VC\%$ (mean 29%, range 21.6–49%). All had been heavy cigarette smokers for many years.

All showed little or no increase in daily PEFR during a course of corticosteroid therapy (at least 20 mg of prednisone daily for at least two weeks). The mean improvement in FEV_1 after inhalation of 100 μg of isoprenaline was 5.6% and the greatest individual improvement was 11%. Six had symptoms of chronic bronchitis using the criteria of the Medical Research Council (1965) and all had noticed increasing dyspnoea on exercise over recent years. No patient had blood or sputum eosinophilia and there was no past history suggestive of asthma. All bronchodilator drugs were withdrawn 12 hours before the study and no patient was studied during or after a recent exacerbation of airflow obstruction.

The following measurements were made prior to bronchodilator therapy:

1. FEV_1, forced vital capacity (FVC) and slow vital capacity (VC) (best of three measurements) using a Godart Pulmotest wet spirometer.
2. Functional residual capacity (FRC) using the closed-circuit multiple-breath helium dilution technique. From this the residual volume (RV) and total lung capacity (TLC) were derived.
3. Maximum expiratory and inspiratory flow–volume loops (MEFV and MIFV respectively) using an Ohio 842 dry spirometer, Telequipment storage oscilloscope physical data transient store and Bryans X-Y recorder. Maximum expiratory and inspiratory flow rates at 50% of FVC (MEF_{50} and MIF_{50} respectively); peak expiratory and inspiratory flow rates (PEFR and PIFR respectively) were derived from the flow-volume loops. In each case the best of three loops was recorded.
4. Pressure–volume studies, using a Godart compliance test P–V recorder, Validyne pressure transducer and Godart Pulmotest wet spirometer to record flow rates and tidal volume. A thin latex balloon, 6.5 cm long, sealed around the end of a polyethylene tube 114 cm long, was used. Nasal mucosa was anaesthetized with lignocaine hydrochloride solution (4%). An estimate was made of the distance between the nares and a point about 10–15 cm from the stomach. The balloon was lubricated with lignocaine gel 1%, filled with 2 ml of air and passed to the predetermined point. Air was removed from the baloon leaving 1 ml and it was connected to the transducer by means of a three-way tap.
5. Dynamic compliance (C dyn); tidal volume (V_T); respiratory frequency (Rf); mid-expiratory and inspiratory pulmonary resistance (R_L ex and R_L insp respectively) were all derived from tidal pressure–volume studies based on the technique of Frank et al. (1957).
6. Transfer factor (TLco) and transfer coefficient (Kco) were measured in three of the patients by the single-breath technique.
7. Exercise tests were performed on an Avionics Treadmill and heart rate measured using an ECG monitor.

All patients inhaled 2 ml (10 mg) of nebulized salbutamol (Ventolin Respirator Solution, 0.5%) administered via a Minineb nebulizer over a period of approximately 10 minutes. The following measurements were then repeated: FEV_1, FVC, slow VC, MEFV and MIFV curves, pressure–volume loop during tidal breathing and an exercise test. It was possible in one patient (5) to examine the acute effect (i.e. within one hour) of nebulized salbutamol on FRC.

Six patients completed a treadmill modification of the 12-minute walk test (McGavin et al. 1976), and three a modified Bruce exercise test. One was unable to complete the exercise because of dizziness. The modified 12-minute walk test, previously described in a study by Wilson and Connellan (1980), consists of setting the treadmill at zero gradient and a comfortable walking speed for the patient, as pre-determined by a short practice walk. The patients were asked to walk for as long as possible and to stop only when they felt unable to continue further without a 'breather'. The distance walked and the number of stops required, during a 12-minute period, were recorded. ECG and heart rate were monitored throughout. This modification was used, so that the ECG and heart rate could be monitored, because all the patients had severe airflow obstruction and were receiving a large dose of bronchodilator.

Statistical significance of post-bronchodilator changes were assessed using a paired *t*-test in all cases.

Table I. Physiological measurements before and after inhalation of nebulized salbutamol

Patient	*FEV_1* (litres)		*VC* (litres)		*PEFR* (litres/sec)		*PIFR* (litres/sec)		*MEF_{50}* (litres/sec)		*MIF_{50}* (litres/sec)		*IC* (litres)	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	0.40	0.40	1.80	2.10	2.4	2.9	2.0	3.1	0.2	0.3	1.4	2.4	1.20	1.30
2	1.60	1.85	3.25	4.10	3.6	5.5	2.6	4.6	0.9	0.9	2.1	3.1	2.20	2.90
3	0.50	0.65	1.50	2.10	1.5	2.6	2.0	3.8	0.3	0.4	1.8	3.5	0.95	1.35
4	0.60	0.70	1.70	3.00	4.2	4.7	4.0	4.8	0.3	0.5	4.1	4.4	1.35	1.90
5	0.80	1.05	2.65	3.70	4.2	5.0	—	—	0.3	0.4	—	—	2.15	2.80
6	0.80	1.00	3.25	4.25	2.7	4.1	2.2	4.5	0.3	0.4	2.2	4.5	2.10	3.10
7	0.45	0.55	1.75	2.40	3.7	3.6	2.0	3.4	0.2	0.3	2.1	2.6	1.00	1.40
8	0.60	0.80	2.55	2.90	4.4	4.5	3.0	4.1	0.2	0.3	2.9	4.0	1.65	2.00
9	0.60	0.60	2.50	3.10	1.7	2.0	3.2	4.1	0.2	0.2	2.7	3.4	1.50	2.10
10	0.55	0.65	2.55	3.40	2.3	3.1	1.9	2.6	0.3	0.3	1.8	2.3	1.65	1.70
Mean	0.69	0.83	2.35	3.10	3.07	3.80	2.54	3.89	0.32	0.40	2.34	3.35	1.58	2.06
± SD	0.35	0.41	0.63	0.77	1.08	1.14	0.72	0.74	0.21	0.20	0.80	0.83	0.46	0.67
P	<0.001		<0.001		<0.01		<0.001		<0.01		<0.001		<0.001	

B = Before and A = 10 minutes after nebulized salbutamol.

RESULTS

Table I shows mean values of pre-bronchodilator lung volumes and demonstrates the severity of airflow obstruction with a mean FEV_1 of 0.69 litres and $FEV_1/VC\%$ of 29%. The mean value of Kco (in three patients only) was 0.5 mmol/kPa/min/litre (1.8 ml/mmHg/min/litre). Mean values ± SD of FRC and TLC for all patients were 4.6 ± 1.07 and 6.2 ± 1.07 litres respectively. After inhalation of salbutamol there was a much greater absolute increase in VC than in FEV_1 (Table I), the mean increases over base-line being 32% for VC, 20.3% for FEV_1 and 30.4% for inspiratory capacity (IC).

In one patient (5), measurements of lung volumes were repeated one hour after bronchodilator and as shown in Fig. 1 there was a reduction in FRC of 1.9 litres and an increase in slow VC of 1.05 litres.

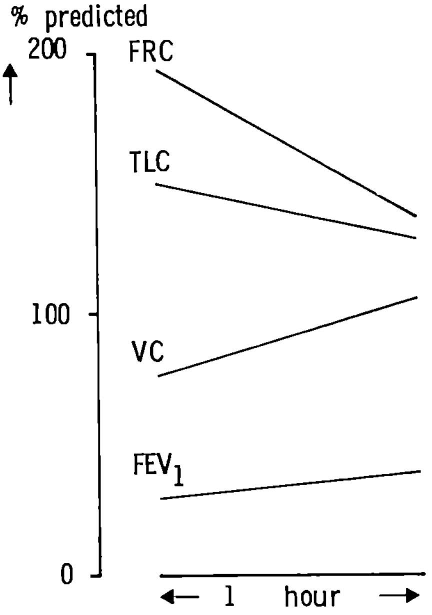
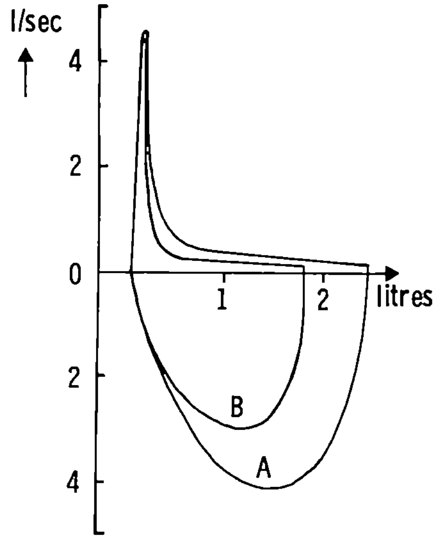


Fig. 1. Change in lung volumes, expressed as a percentage of predicted value, in one patient (5), one hour after bronchodilator

Fig. 2 shows an example of flow–volume loops measured in another patient (8) before and 10 minutes after bronchodilator. The mean values of PEFR, PIFR, MEF_{50} and MIF_{50} (before and after bronchodilator) for all patients are shown in Table I. Although there were mean improvements in expiratory flow rates as shown by FEV_1 (20.3%), PEFR (23.8%) and MEF_{50} (25%) these were all on very low base-line values (see absolute values, Table I). There were much greater proportionate increases in the inspiratory variables as shown by IC (30.4%), PIFR (53%) and MIF_{50} (43%).

Fig. 3 is an example of pressure–volume loops measured in another patient (7) during tidal breathing before and 10 minutes after bronchodilator. The mean values of V_T, Rf, mid-inspiratory and expiratory pulmonary resistance and dynamic compliance during tidal breathing before and 10 minutes after bronchodilator for all the patients are shown



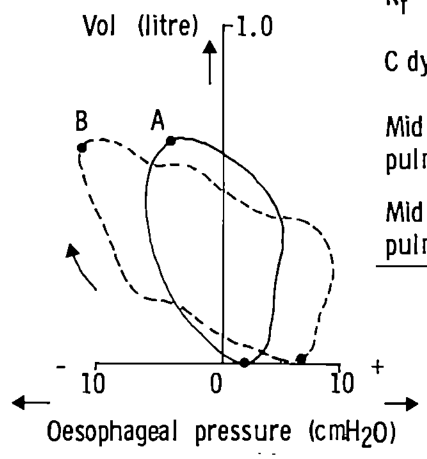
	B	A
PEFR	4.4 l/sec	4.5
PIFR	3.0	4.1
MEF_{50}	0.15	0.3
MIF_{50}	2.9	4.0

B = Before

A = After nebulised bronchodilator

Fig. 2. Flow–volume loops measured in one patient (8) before and 10 minutes after bronchodilator. Each loop was drawn as a best fit from the best of three loops

in Table II. There was a small mean increase in tidal volume of 94 ml which just reached significance ($P=0.05$); respiratory rate dropped by a mean of < 1 breath/minute (non-significant) and there were statistically significant decreases in $R_L$ex and $R_L$insp. Dynamic compliance measured five minutes after bronchodilator increased in all of the patients



	B	A
V_T	550 mls	550
R_f	17 /min	17
C dyn	0.0385 l/cmH_2O	0.143
Mid expiratory pulmonary resistance	43 $cmH_2O/l/sec$	26
Mid inspiratory pulmonary resistance	10 $cmH_2O/l/sec$	9.1

B = Before bronchodilator

A = After bronchodilator (10 min)

● = points of zero flow

Fig. 3. Pressure–volume loops measured in one patient (7) during tidal breathing before and 10 minutes after bronchodilator. Each loop was drawn as a best fit from the tidal pressure-volume tracing when the spirometric pattern was stable. The curved arrow indicates inspiration

and the improvement was maintained at 10 minutes in seven of them, values in the other two having reverted to pre-bronchodilator levels (see Table II). This improvement in dynamic compliance and pulmonary resistance implies that the inspiratory work of breathing was less after bronchodilator.

Each patient (except 5) had an exercise test before and after bronchodilator. Walk distance improved in eight of the nine. Table I shows the increases in walk distance in the six patients who performed the modified 12-minute walk test. There was on average a 56% increase over base-line in walk distance.

Table II. Physiological measurements before and after inhalation of nebulized salbutamol

Patient	V_T		Rf		R_L ex		R_L insp		C dyn		*12 MD*	
	B	A	B	A	B	A	B	A	B	A	B	A
1	950	850	9	9	23.0	20.0	20.0	8.2	0.055	0.055	186	425
2	450	550	18	19	20.5	13.0	11.5	6.0	0.061	0.061		
3	600	650	15	18	17.0	10.0	4.6	3.5	0.039	0.055		
4	500	700	19	20	16.0	10.0	5.5	3.8	0.120	0.280		
5	700	900	16	12	22.0	15.0	10.0	5.5	0.099	0.209		
6	800	1000	16	13	48.0	14.0	10.9	6.1	0.044	0.110	153	234
7	550	550	17	17	43.0	26.0	10.4	9.1	0.039	0.143	75	115
8	800	1050	12	12	26.5	13.5	9.9	6.2	0.080	0.132	207	251
9	650	600	14	12	69.0	36.0	15.6	8.4	0.033	0.072	50	61
10*											224	335
Mean	667	761	15.1	14.7	31.7	17.5	10.9	6.3	0.063	0.124	149	240
±SD	162	193	3.1	3.9	17.9	8.6	4.7	1.9	0.03	0.08	72	138
P	0.05		NS		<0.01		<0.01		<0.01		<0.05	

* Patient unable to tolerate p-v study.

Tidal pressure-volume measurements before (B) and 10 minutes after (A) bronchodilator. V_T = tidal volume (ml); Rf = respiratory frequency (breaths/min); $R_L$ex and $R_L$insp = mid-expiratory and inspiratory pulmonary resistance (cmH$_2$O/litre/sec); C dyn = dynamic compliance (litres/cmH$_2$O); 12-MD = 12-minute walking distance (yards).

Mungall and Hainsworth (1979) have shown that the 12-minute walk distance is very reproducible provided the first two walks are ignored. We repeated the modified 12-minute walk test on five patients and noted very similar improvements. One patient (1), who had improved his walk distance after bronchodilator on two previous occasions, offered a good opportunity to look for any placebo response. He was told that he would receive the same therapy on this occasion but that a third walk using a different dose would be added. His pre-therapy walk distance was 440 yards, after nebulized saline (2 ml) it was 380 yards and after nebulized salbutamol (10 mg) 580 yards.

DISCUSSION

Miller et al. (1965) reported evidence which suggested that the work of breathing was reduced in patients with emphysema after treatment with nebulized bronchodilator. They noted a consistent reduction in inspiratory airflow resistance but little change in

FEV_1, FVC or FRC. O'Connell and Campbell (1976), in a study of lung mechanics in airflow obstruction associated with 'inspiratory dyspnoea', noted that this association occurred predominantly in severe airflow obstruction and that these patients were using a high proportion of inspiratory muscle strength during quiet breathing. They argued that an increase in available muscle strength would occur if FRC decreased when airways resistance was lowered. Marshall et al. (1954) found that the sensation of dyspnoea was related to the pressure exerted upon the lungs and Nisell (1960) found that, in exercise, dyspnoea was related to the magnitude of the intra-oesophageal pressure fluctuations.

In this study, 10 patients were selected who on usual criteria would be considered to have severe irreversible airflow obstruction. All claimed some relief of dyspnoea after nebulized bronchodilator. Inspiratory flow rates (PIFR and MIF_{50}), slow VC and IC improved to a greater extent than FEV_1 and other expiratory flow rates. Mid-expiratory and inspiratory pulmonary resistance and dynamic compliance derived from tidal pressure–volume loops also improved with bronchodilator and these improvements were not due to a change in respiratory frequency. The duration of this effect was not fully established but in one patient (5), improvements in VC and FRC were noted one hour after bronchodilator and the relief of dyspnoea, claimed by all the patients, lasted 1 to two hours.

The improvement in exercise tolerance correlated more closely with slow VC than with FEV_1 and this is in agreement with the findings of McGavin et al. (1976). It is possible that some of this improvement is due to a reduction in pulmonary resistance and FRC resulting in increased mechanical advantage to inspiratory muscles and reduction in the inspiratory work of breathing.

It is suggested that, when looking for evidence of reversibility in patients with severe airflow obstruction, useful additional information may be obtained simply by measuring slow VC, maximum inspiratory flow rates, inspiratory capacity and exercise tolerance before and after bronchodilator. The dose and method of administration required to achieve maximum benefit and duration of effect, safely, in patients with severe airflow obstruction, remain to be established.

ACKNOWLEDGEMENTS

We are indebted to Dr R. S. E. Wilson whose original and current research has formed the basis of this study. We are grateful to Dr L. C. Lum, Dr J. E. Stark and Dr N. B. Pride for encouragement and advice and to Penny Edmonds for typing the manuscript.

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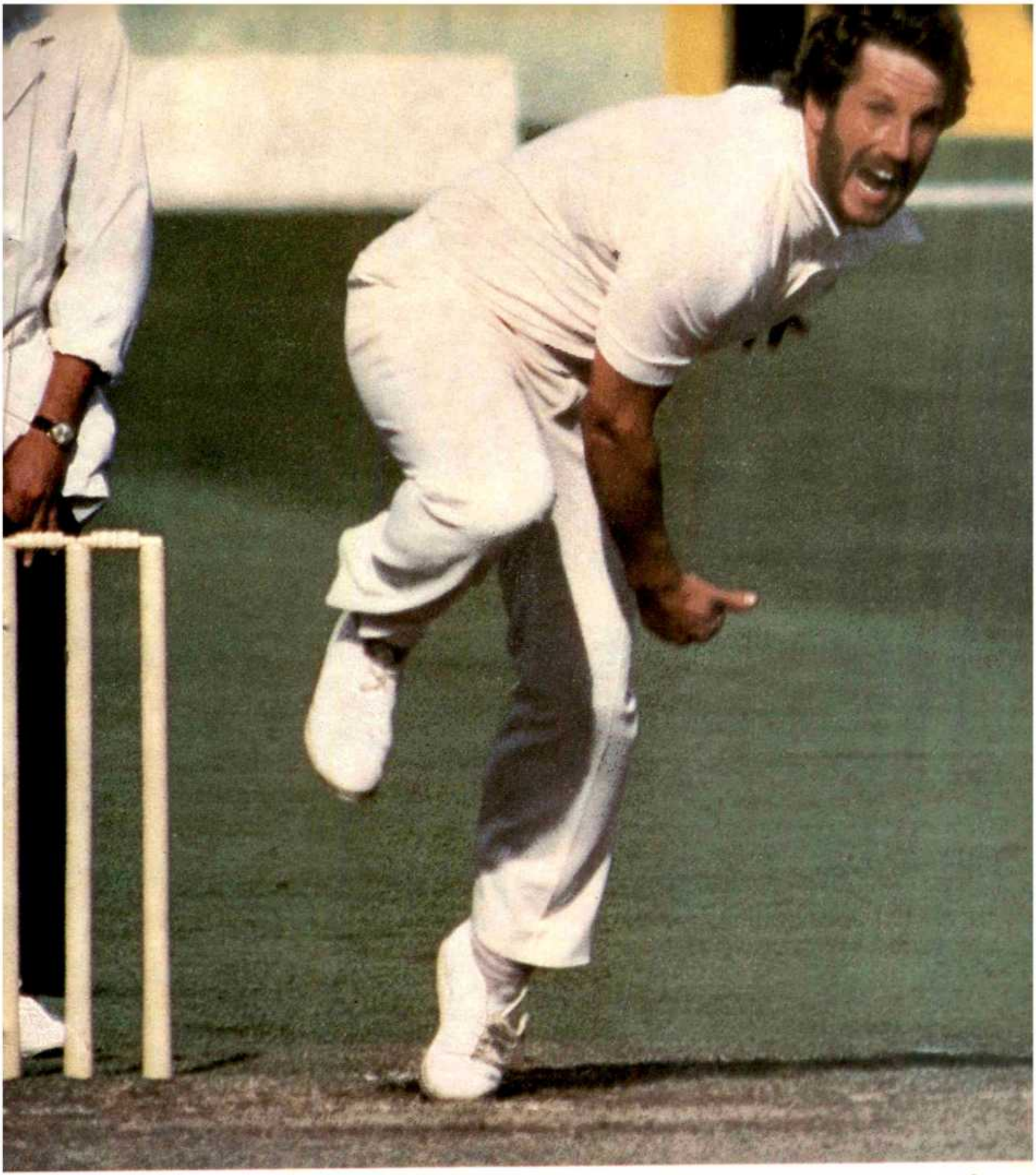

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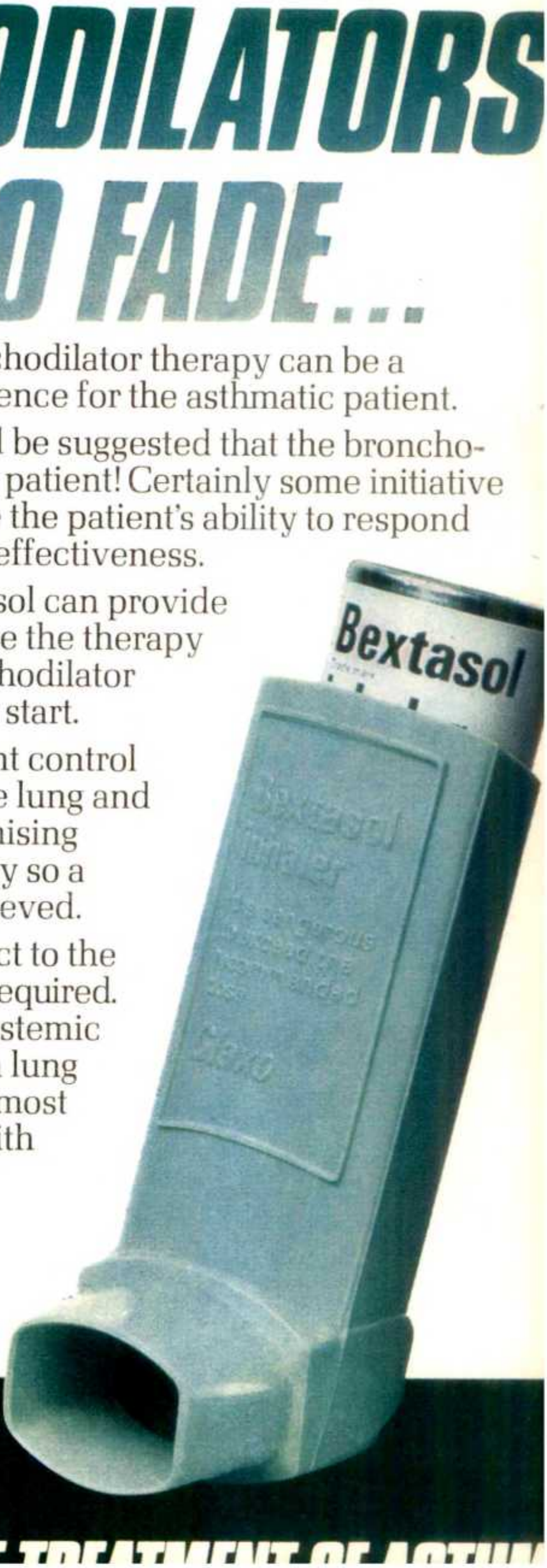

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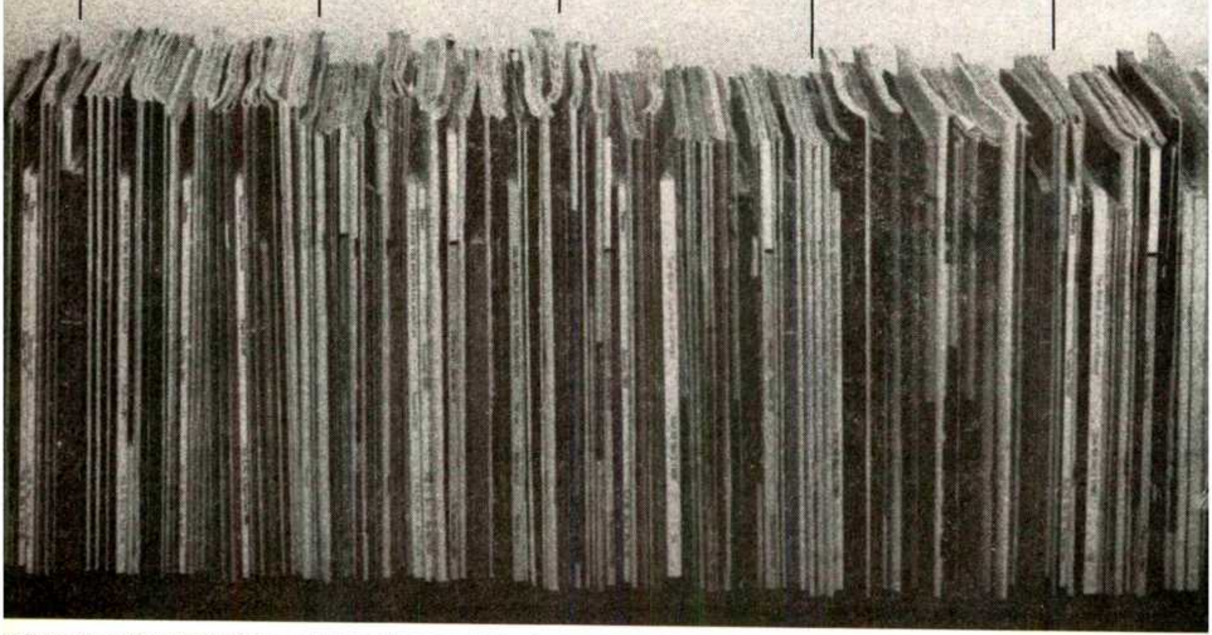

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Br. J. Dis. Chest (1982) 76, 143

RESPONSES TO CIGARETTES OF VARIOUS TAR CONTENTS

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Summary

Specific conductance was measured before and within ten minutes of smoking a cigarette in 36 smokers on 210 occasions. Five types of cigarette were used including the equivalent of a 1956 unfiltered cigarette. Cigarettes were smoked in the smokers' usual fashion. Significant decreases in specific conductance occurred on only 19 occasions in 13 subjects and were most frequent with the cigarette with the highest tar content currently available. Examining the overall results the only significant change was an increase in specific conductance in the control, non-smoking period.

We conclude that irritant qualities of tobacco smoke increase with tar content but airway narrowing lasting up to ten minutes is an uncommon event when cigarettes are smoked normally. Most smokers adapt to or avoid any sustained acute airway response to tobacco smoke whatever its tar content.

INTRODUCTION

Most cigarettes currently sold in Great Britain and in the United States are filter cigarettes and the average tar and nicotine content of these has slowly decreased (Capell 1978). Coincident with these changes there has been a marked decrease in the bronchial epithelial changes of smokers at autopsy (Auerbach et al. 1979). Smokers who are unable to stop smoking completely are commonly recommended to change to a brand with a lower tar and nicotine content in order to decrease their risk of smoking-related diseases.

A number of previous reports have indicated that after smoking in a normal manner few subjects show significant airway narrowing (Clarke et al. 1970; Higenbottam et al. 1980*a*, *b*) but only small numbers have beeen involved in some of these studies. Variation in the prevalence of airway narrowing may relate to characteristics of the subjects (Higenbottam et al. 1980*a*), method of smoking (Higenbottam et al. 1980*b*) or the type of cigarette (Da Silva & Hamosh 1980). We have investigated responses to a normal pattern of smoking in 36 smokers with cigarettes of various tar contents.

Materials and Methods

Subjects

Thirty-six male subjects were studied. All had smoked for at least two years and were currently smoking between 10 and 40 cigarettes per day. The study was divided into six two-week periods and each subject was studied once in each period at the same time of day. One group of six subjects performed the study twice in an attempt to assess the repeatability of the responses.

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Cigarettes

Five brands of cigarette were used. Three (B, C, E) covered most of the range now available on the United Kingdom market, the (D) was a 1956 unfiltered Players Medium cigarette and one (A) was a cigarette containing 35% New Smoking Material. The characteristics of the cigarettes are shown in Table I. The sixth session was a control period during which the subjects did not smoke but went through the same sequence of measurements. All subjects were asked to refrain from smoking for at least one hour before coming to the laboratory. The order of the six periods was randomized in a six by six Latin Square design. Subjects were allowed to sit quietly and smoke in their usual fashion with no constraints.

Table I. Changes in logsGaw after smoking five different cigarettes and after a non-smoking period

Cigarette	*Filter*	*Particulate matter* (mg)	*Nicotine* (mg)	*New smoking material*	*% of subjects with significant changes*		*Subjects with significant changes in sGaw*	
					Increase	Decrease	Increase	Decrease
A	+	15	1.0	+	10	2	11, 12, 28, 33a	13
B	+	13	0.7	–	5	7	18, 19	9, 13, 21
C	+	17	1.3	–	5	10	3, 7	6, 15, 20, 25
D	–	34	3.6	–	5	17	30, 33a	8, 13, 15, 21 29, 33b, 35a
E	–	35	?	–	5	10	4, 36b	15, 16, 20, 23
F	Non-smoking control period				14	0	5, 10, 11, 24 29, 35b	

Thirty-six subjects were studied; subjects 31 to 36 were studied on two occasions, suffixed a and b.

Measurements

Airways resistance was measured in a constant volume body plethysmograph by the method of DuBois et al. (1956). Recordings of flow against box pressure and mouth pressure against box pressure were made and the slopes subsequently measured by an experienced observer unaware of the order of the recordings. Nine measurements of airways resistance and lung volume were made before the smoking period. After smoking the subject returned to the plethysmograph and three estimations of airways resistance were made within four minutes of finishing smoking. Three further measurements were made during the next five minutes.

Analysis

Results in each individual were analysed by an analysis of variance technique comparing the nine measurements before smoking with the six after. There was a significant change in thoracic gas volume on at least one occasion in 24 of the 36 subjects; therefore airways resistance was converted into specific airways conductance (sGaw) and the logarithmic transformation (logsGaw) was used as it is approximately normally distributed (Guyatt & Alpers 1968). Overall changes for all 36 subjects were compared by paired *t*-tests.

RESULTS

Significant changes in logsGaw were uncommon; it decreased below the 95% confidence limits on 19 occasions in 13 subjects out of the 210 periods during which a cigarette was smoked. Two subjects had a significant decrease in logsGaw with three different cigarettes. The distribution of the changes after the six periods is shown in Table I. There was a greater number of significant decreases in logsGaw with increased tar content of the currently available brands. Compared with current brands, the 1956 style Players (D) produced changes no more frequently than would be expected from chance variation. The presence of New Smoking Material (A) did not affect the responses. During the control no smoking period there were no significant decreases in logsGaw although significant increases were found on six occasions. The greatest change seen on smoking was a 50% decrease in sGaw.

Mean values of logsGaw before and after each group of 42 exposures are shown in Fig. 1. The only significant change was an increase in logsGaw over the non-smoking period (F) ($t = 2.10$, $P < 0.05$).

Of the six subjects studied on two occasions only two showed significant airway narrowing. This occurred with the middle to high tar cigarette (D) and, in each subject, was found on only one of the two occasions this cigarette was smoked.

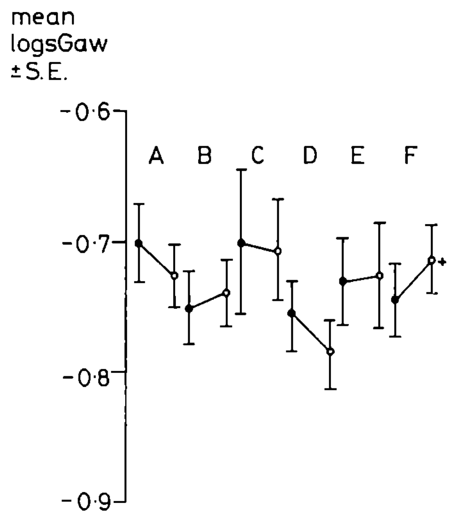

Fig. 1. The mean values of logsGaw before (●) and after (○) 42 smoking periods. Letters A to E represent the cigarettes shown in Table I and F the non-smoking period. + = $P < 0.05$

DISCUSSION

There is disagreement between previously reported studies regarding the number of subjects who develop significant airway narrowing on smoking a cigarette. When subjects are analysed individually after smoking one cigarette in a normal manner the most common finding is of significant change in only a minority of subjects (Clarke et al. 1970; Higenbottam et al. 1980*a*, *b*). Some of the studies showing more frequent bronchoconstriction have used an abnormal manner of smoking (Nadel & Comroe 1961; Reintjes et al. 1972; McCarthy et al. 1976; Hamosh & Da Silva 1977).

Since filtration of cigarette smoke affects the responses (Clarke et al. 1970; Da Silva & Hamosh 1980) the constituents of the cigarette smoke are evidently important. Details of the cigarettes used are often omitted from the reports in the literature but our findings using a 1956-style Players Medium cigarette suggest that changes in cigarettes over the last 25 years do not account for the variation between studies.

The results reported here show that when airways resistance measurements are made three to ten minutes after smokers have smoked a ciagarette in their usual fashion significant bronchoconstriction is uncommon. In this study such airway narrowing was found in only 9% of patients. There did appear to be a relationship to the type of cigarette smoked, in that the frequency of changes increased with increasing tar content from low to middle to high tar. The addition of New Smoking Material to the cigarettes did not affect the results.

In the control period during which the subjects did not smoke there was a tendency for a small degree of bronchodilatation to occur. Therefore, the procedures themselves are unlikely to be responsible for any airway narrowing detected.

If the airway narrowing is a protective reflex then the sooner it occurs after the first exposure to the inhaled irritant the more effective it is likely to be. Measurements made within the first minute of cigarette smoke inhalation show that bronchoconstriction is found in most subjects even after single inhalations of smoke (Rees et al. 1982). Such changes are, however, transient, usually lasting less than one minute.

Our results suggest that cigarettes with a high tar content may be more irritant to the airways. However, significant airway narrowing lasting up to ten minutes after smoking is uncommon when regular smokers smoke cigarettes in their usual fashion. Consequently such measurements are unlikely to be useful in investigating the irritant properties of tobacco smoke. It is also unlikely that chronic airflow obstruction seen in some smokers results from the persistence of repeated episodes of acute reflex airway narrowing. Rather the chronic airflow obstruction is likely to be caused by structural changes in the airways as a result of repeated and long term exposure to inhaled smoke.

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BLUNTED SYMPATHOADRENAL RESPONSE TO EXERCISE IN ASTHMATIC SUBJECTS

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Summary

Six asthmatic subjects and six matched controls performed a standardized exercise test in which resting and post-exercise blood samples were assayed radioenzymatically for catecholamines. Plasma adrenaline one minute after exercise rose over threefold in the controls whereas in the asthmatic subjects there was no increase. Plasma noradrenaline increased to five times the basal concentration in the controls, but to less than half this level in the asthmatic subjects. These results agree with a recent study (Barnes et al. 1981) and suggest there is a marked abnormality of the sympathoadrenal response to exercise in asthmatic subjects.

Introduction

Plasma catecholamine concentration increases in normal subjects on exercise (Winder et al. 1978; Barnes et al. 1981) but it has recently been suggested that asthmatic subjects fail to show a rise in plasma adrenaline on exercise (Reinhardt et al. 1980; Barnes et al. 1981). We have attempted to confirm these findings since they differ from those of previous studies (Griffiths et al. 1972; Beil et al. 1977; Chryssanthopoulos et al. 1978; Zielinski et al. 1980).

Materials and Methods

Six atopic asthmatic subjects, all of whom had previously required in-patient treatment for acute asthma, underwent the same exercise test as six non-atopic control subjects. None of the subjects had previous experience of exercise testing. The asthmatic subjects were asymptomatic before the study, had taken no medication in the 12 hours preceding the study and were not receiving steroid therapy. In each group there were three males and three females. The mean age of the asthma group was 26 years (range 19–32) and of the control group 26 years (range 24–28). There was no significant difference in height or weight between the two groups.

The subjects were rested and an indwelling venous catheter inserted 30 minutes before they started exercising. Except for the six-minute exercise period, the subjects remained seated throughout. Blood was taken, and peak expiratory flow rate (PEFR) and pulse rate measured, 15 and five minutes before the start of exercise. These procedures were repeated one, three, five and 20 minutes after exercise. Exercise was performed on a treadmill for six minutes at an incline of 15°. The speed of the treadmill was between 5 and 10 kph and was adjusted to each individual's physical fitness. Blood was collected and immediately put on ice. It was centrifuged at 0°C and plasma stored at −80°C within 30 minutes of being taken. Plasma catecholamines were measured by a radioenzymatic method (Da Prada & Zurcher 1976) with a sensitivity of 0.05 nmol/litre. Intra- and inter-assay coefficients of variation were 3.7 and 5.8% respectively.

RESULTS

There was no significant difference between the groups in mean treadmill speed or in the pulse rate in the first minute after exercise. In the asthmatic group the pulse rate immediately after exercise was 170 ± 8.0 beats/minute and in the control group 175 ± 7.6 beats/minute (mean ± SEM). The mean PEFR ± SEM before exercise of the asthmatic group was 432 ± 33 litres/minute and of the control group 574 ± 39 litres/minute. After

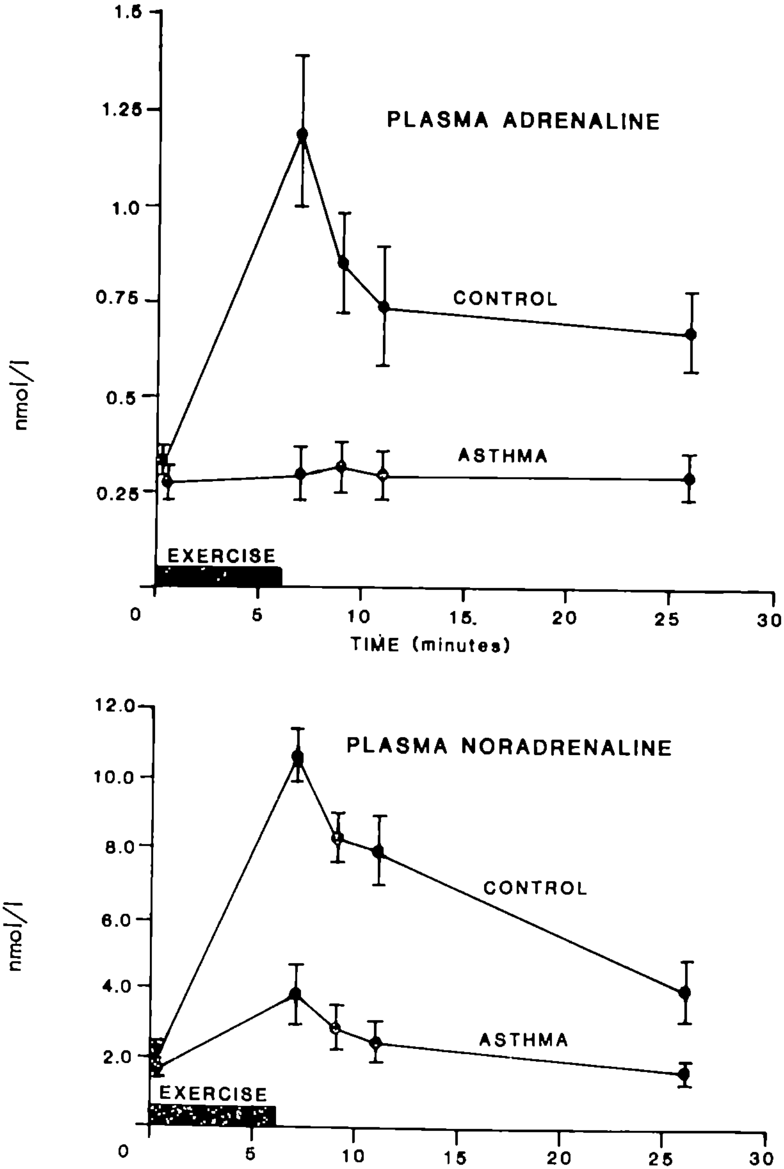

Fig. 1. Plasma adrenaline and noradrenaline concentrations before and after exercise in asthmatic and control subjects. Each point represents the mean ± SEM for six subjects

exercise this fell in the asthmatic group to 299 ± 50 litres/minute but did not change significantly in the controls.

In the control group the resting plasma noradrenaline and adrenaline were 2.19 ± 0.18 and 0.33 ± 0.04 nmol/litre respectively (mean ± SEM). In the asthmatic group the resting values were not significantly different from those of the controls (noradrenaline 1.71 ± 0.18, adrenaline 0.28 ± 0.04 nmol/litre). One minute after exercise there were the expected rises in plasma noradrenaline and adrenaline in the control group to 10.63 ± 0.59 and 1.19 ± 0.19 nmol/litre respectively (Fig. 1). However, in the asthma group there was no significant increase in plasma adrenaline after exercise and the plasma noradrenaline concentration was at all times significantly less than in the controls ($P < 0.01$), being 3.84 ± 0.89 nmol/litre one minute after exercise.

DISCUSSION

The blunted noradrenaline and absent adrenaline response to exercise suggests an abnormality of the sympathoadrenal system in patients with asthma.

The difficulties experienced in developing a sensitive and specific assay technique for catecholamines (Cryer 1980) may explain why previous studies using fluorometric methods show results dissimilar to our own (Griffiths et al. 1972; Beil et al. 1977; Chryssanthopoulos et al. 1978; Zielinski et al. 1980).

A recent study (Reinhardt et al. 1980) using a radioenzymatic assay showed that serum adrenaline failed to rise with exercise in all but one of 17 asthmatic children, although this was not compared with control subjects. The first study to compare the catecholamine response to exercise in asthmatic subjects to that of controls using a radioenzymatic assay (Barnes et al. 1981) showed similar results but in addition showed a failure of catecholamines to rise with hyperventilation in either asthmatic or control subjects.

It has been suggested that one of the functions of the adrenal medulla is to counteract pathological processes or products which tend to produce bronchoconstriction (Jackson 1912). Early morning wheezing correlates with the nadir of plasma adrenaline's circadian rhythm and a peak in plasma histamine (Barnes et al. 1980). Therefore it has been suggested that asthmatic subjects have an inadequate adrenergic response to bronchoconstrictor stimuli (Drazen 1980). If the plasma histamine concentration rises on exercise (Anderson et al. 1981), possibly together with other mediators, it may be the absence of the protective effect of a rise in adrenaline secretion that results in bronchoconstriction in the asthmatic subject. This is supported by the sensitivity of asthmatic subjects to beta-blocking drugs and the effectiveness of beta-sympathomimetics in preventing exercise induced asthma (Jones et al. 1963). The failure of plasma adrenaline to rise with exercise in patients with asthma may therefore play a part in the pathogenesis of exercise-induced asthma.

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COMPLICATIONS OF INTRAPLEURAL BCG IN THE TREATMENT OF OPERABLE NON-SMALL-CELL BRONCHIAL CARCINOMA

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Summary

Seventy-eight patients entered a randomized study of postoperative intrapleural BCG in the treatment of bronchial carcinoma. 39 patients received BCG (Tice strain), of whom 17 took isoniazid, and there were 39 controls. There was a high rate of complications related to the use of intrapleural BCG, in both isoniazid and non-isoniazid treated groups. Postoperative infections occurred in eight BCG treated patients and one control; seven BCG treated patients but only one control developed prolonged postoperative chest pain. Empyema developed six months postoperatively in three of the BCG treated group. Furthermore BCG conferred no survival advantage at one year. We considered the complications to be of sufficient severity and incidence to discontinue the study.

INTRODUCTION

It has been reported that patients with bronchial carcinoma who survive postoperative empyema have a lower incidence of local relapse than patients with an uncomplicated postoperative recovery (Takita 1970; Ruckdeschel et al. 1972). This supported the concept that the immune system might be induced by an infective or other stimulus to destroy residual small intrathoracic deposits of tumour. The effectiveness of bacillus Calmette Guérin (BCG) as an immunostimulant was first established by Old et al. (1959). However, intradermal administration of BCG has been found not to prolong survival in bronchial carcinoma (Edwards 1979; Pouillart et al. 1979; Stack et al. 1979; Millar et al. 1980). Animal studies indicated that the greatest benefit is obtained from BCG when it is administered to the tumour site after surgical reduction of tumour bulk to a minimum (Bast et al. 1974; Laucius et al. 1974). McKneally et al. (1976*a*, *b*, 1978) reported that a single intrapleural injection of BCG (Tice strain) given after resection of bronchial carcinoma together with oral isoniazid 300 mg daily from the third to the fourteenth week, prolonged the survival of patients with localized disease. Other studies have failed to confirm improvement in survival associated with the use of intrapleural BCG in bronchial carcinoma (Jansen et al. 1980; Lowe et al. 1980), possibly because a different strain of BCG was used. There is evidence from animal work that Tice BCG (used by McKneally et al.) is more immunogenic than Glaxo strain (Mackaness et al. 1973; Wilmott et al. 1977). Tice and Pasteur strains have been compared in the treatment of malignant melanoma and significant prolongation of survival found only with Tice strain (Gutterman et al. 1973).

The purpose of the present study therefore was to attempt to confirm prolongation of survival in bronchial carcinoma with Tice BCG given intrapleurally, using the methods of McKneally et al. (1976*a*, *b*). However, a high incidence of complications has been encountered, of sufficient severity to discontinue the study. This report describes the complication and survival to date.

Methods

Patients having surgery for non-small-cell carcinoma of the bronchus were randomly allocated to BCG treated and control groups by a sealed envelope technique. The treated patients received 10^7 viable units of Tice BCG intrapleurally four to seven days postoperatively. Diluted vaccine was injected either directly into the pneumonectomy space or, in those who had undergone lobectomy, into the chest drain immediately before its removal. Strict aseptic technique was followed.

The BCG treated patients were further randomized to groups treated and not treated with oral isoniazid, in order to assess whether a more prolonged action of BCG might further enhance any survival benefit conferred by the BCG. Isoniazid treated patients took 300 mg daily from the third to the fourteenth week. Control group patients took neither isoniazid or placebo.

As in previous studies (McKneally et al. 1976*b*; Lowe et al. 1980), tumours were divided into three stages. Stage 1 included all tumours confined to the lung and those of less than 3 cm diameter with hilar lymph node metastasis. Stage 2 tumours were more than 3 cm in diameter with hilar node metastasis and Stage 3 had invasion of mediastinal structures or chest wall or metastasis to mediastinal lymph nodes.

RESULTS

Intrapleural BCG was administered to 39 patients, of whom 17 took isoniazid, and there were 39 control patients. 22 from each group had Stage 1 tumours and 17 from each group had Stage 2 or 3 tumours. The BCG treated patients had a mean age of 61 years (range 40–74) and the control group a mean age of 60 years (range 36–65). There were 31 males in the BCG treated group and 32 in the the control group. The mean period of follow-up was 13.3 years for the BCG group and 13.8 years for the control group. 13 patients of each group had a pneumonectomy and 26 a lobectomy. 22 patients in the BCG group and 23 in the control group had squamous carcinoma, eight in each group had adenocarcinoma, large cell carcinoma was found in six BCG treated and five control patients and undifferentiated carcinoma in three patients in each group.

Complications

Postoperative infections. Eight BCG treated patients developed postoperative infections (apparent within two weeks of surgery). Five had wound infections and three empyema; one patient died of postoperative empyema. Pyogenic organisms were cultured from one case with wound infection and two with empyema; no organism was cultured in the remaining cases. One control group patient had a bacterial empyema. The incidence of eight postoperative infections among 39 BCG treated patients compared to one among controls was statistically significant ($P < 0.01$).

Delayed empyema. Three of the BCG treated patients developed a delayed empyema. Symptoms developed insidiously within a few weeks of operation. These three patients had had a pneumonectomy; in each case the pneumonectomy space fluid was clear when previously aspirated during the earlier stages of the illness and did not become purulent until six to seven months postoperatively. Aerobic and anaerobic cultures of the purulent fluid were negative. Acid-fast bacilli (AFB) were seen on smear in two cases: in pneumonectomy space fluid in one and in open biopsy material from the chest wall in the other (the pneumonectomy space fluid having been repeatedly negative for acid-fast bacilli in this case). Cultures for BCG in these three patients have been negative, but triple antituberculous therapy was commenced. In the first case there has been time to assess response, and the severe chest pain and ESR of 91 mm/hour have subsided.

Prolonged postoperative chest pain. Seven BCG treated patients developed prolonged chest wall pain. The pain in these cases was more severe than would be expected from the surgical incision, required regular analgesics and did not relate to chest wall invasion by tumour, wound infection or empyema. It became troublesome by the second month and persisted for at least two months. One of these patients (who had been treated with isoniazid) died at 14 weeks and at autopsy widespread granulation tissue was found in the pleural cavity and mediastinum.

Only one of the control group cases had undue pain and the incidence of seven cases in the BCG treated group was statistically significant ($P < 0.025$).

Table I. Summary of complications

Group	*Postop. wound infections and empyema*	*Delayed empyema* (6 months)	*Prolonged chest pain*	*Prolonged fever*
BCG alone ($n = 22$)	5	2	3	0
BCG and isoniazid ($n = 17$)	3	1	4	2
Control ($n = 39$)	1	0	1	0

Other side effects. Two patients had severe pain during and shortly after the injection of BCG, and a number of others had moderate pain. The pain was of short duration and did not relate to later complications.

Disturbed liver function tests, not related to isoniazid and suggestive of granulomatous hepatitis, as described by Hunt et al. (1973), occurred in two cases. There was a febrile reaction after the administration of BCG in 31 cases. It lasted one or two days in 19, three days to two weeks in 10 and over a month in two cases.

These complications are summarized in Table I and their distribution between isoniazid and non-isoniazid treatment groups is shown. Major complications (postoperative infections, delayed empyema and prolonged chest pain) affected 18 of the 39 BCG treated patients, but only two of the controls. Isoniazid did not protect against any of the complications. Complications were evenly distributed between the different histological types.

Survival

The relapse rate amont BCG treated and control patients is shown (Table II). Among the deaths in BCG treated patients, one patient (Stage 3) who died of postoperative empyema and one patient (Stage 1) who died suddenly in the postoperative period, probably from pulmonary embolism, are included. The remaining 11 deaths were from disseminated malignancy.

Table II. Recurrence rate (number of patients dead, or alive with recurrence of tumour)

Group	*Mean follow-up* (months)	*Stage 1* Total	Recurrence	*Stages 2–3* Total	Recurrence
BCG treated ($n=39$)	13.3	22	9 (4 dead)	17	13 (9 dead)
Control ($n=39$)	13.8	22	5 (3 dead)	17	9 (7 dead)

DISCUSSION

Complications of intrapleural BCG have not been reported as a major or common problem in previous studies. Lowe et al. (1980) described one delayed BCG-related wound infection among 48 treated patients and Jansen et al. (1980) one BCG empyema among 17 patients. Neither of these studies used Tice BCG. The complications reported by McKneally et al. (1978) were numerically similar in their group treated with Tice BCG and their control group, but did include six infections in 47 BCG treated patients (five postoperative wound infections and one delayed empyema) and none among controls. Complications were not mentioned in the preliminary report from the North-West Oncology Group by Wright et al. (1978).

In the present study, 18 of the 39 BCG treated patients developed major complications. Despite failure to culture the organism, we consider the BCG infections may have caused the delayed empyemas. Two of the three cases of delayed empyema were smear-positive for acid-fast bacilli and the rarity of bacterial empyema so long after surgery, the insidious nature of the symptoms and the response to antituberculous therapy all suggest that the BCG was causal. The prolonged chest wall pain may relate to a chronic pleurisy induced by BCG, as suggested by the widespread granulation tissue apparent at autopsy in one case and the prolonged pain which occurred in one of the smear-positive empyema cases before the pneumonectomy space fluid became purulent. The postoperative infections were apparent within two weeks and seem more likely to represent pyogenic than BCG infection. However, the increased incidence in the BCG treated group is statistically significant. It is conceivable that, rather than stimulating the patient's immune response to his tumour, the BCG has in some way impaired his response to pyogenic organisms. Isoniazid failed to protect against any of the complications.

The original reports by Takita (1970) and Ruckdeschel et al. (1972) that postoperative empyema improved long-term survival in bronchial carcinoma were based on a small number of cases (14 and 18 respectively). Two larger studies have convincingly refuted this claim (Goldstraw 1980; Minasian et al. 1978). The most recently available figures of McKneally et al. (1981) still show significantly improved survival of patients with Stage 1 tumours given intrapleural Tice BCG (recurrence of tumour in 11 of 36 BCG treated patients and 20 of 36 controls. The preliminary report of Wright et al. (1978) has not confirmed prolongation of survival with Tice BCG, although patients with Stage 1 tumours have not yet been separately assessed. Glaxo BCG has been shown not to prolong survival (Lowe et al. 1980). In the study of Jansen et al. (1980), survival of the control group was unusually poor (16 of 20 died within a year and the longest survivor died at 28 months). Patients treated with intrapleural BCG did not survive longer than another group given intradermal BCG and other studies have failed to show benefit from intradermal BCG in bronchial carcinoma. In the present study, survival was worse in BCG treated patients than in controls, especially in Stage 1 cases, with recurrence or death in nine BCG treated and five control patients. Despite the short follow-up period to date, it is most unlikely that the BCG treated group will eventually achieve significantly better survival than the control group.

We are unable therefore to confirm the claim of McKneally et al. that intrapleural BCG prolongs survival. We considered the complications we encountered to be of sufficient severity to discontinue the study. If patients are given intrapleural BCG, they should be carefully observed and complications treated with triple antituberculous therapy.

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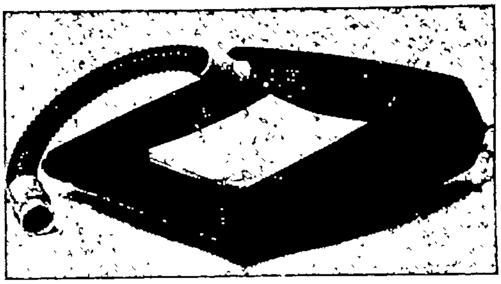

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THE SPEED OF ONSET AND SEVERITY OF ACUTE SEVERE ASTHMA

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Summary

The speed of onset of attacks of acute severe asthma was prospectively studied in a total of 261 consecutive episodes. 82% of these episodes involved patients with 'extrinsic' asthma and 28% involved children. The speed of onset of an attack was rapid (defined as less than 24 hours) in 46% of episodes and was less than one hour in 13%. Rapid-onset attacks occurred more frequently in younger patients and were no more or less severe than attacks of slower evolution. Comparison of different measures of severity in our patients showed statistically significant but low correlations. Objective measures seemed no better than simple clinical assessment with the Jones index. We discuss the significance of these correlations and the place of emergency admission services for attacks of acute severe asthma of rapid speed of onset.

Introduction

There have been conflicting reports on the speed of onset of attacks of acute severe asthma, resulting in different approaches to management. While some workers have stressed the suddenness of onset (Speizer et al. 1968; Macdonald et al. 1976*a*; Ormerod & Stableforth 1980) and advocated self-admission services (Crompton & Grant 1975), others have suggested that the episode often follows a prolonged period of poor control (Bellamy & Collins 1979; Davis et al. 1980) and that improved domiciliary treatment during this period might reverse potentially fatal attacks (Editorial 1979).

Clinical assessment of the severity of an acute severe asthma attack can be difficult and poor assessment has been associated with asthma deaths occurring outside hospital (Macdonald et al. 1976*a*; Ormerod & Stableforth 1980) as well as within (Cochrane & Clark 1975; Macdonald et al. 1976*b*). Objective measurements such as peak expiratory flow rates (PEFR) have therefore been encouraged (Seaton 1978) and the quantitative value of tachycardia (Cooke et al. 1979) and pulsus paradoxus (Knowles & Clark 1973) has been emphasized. We have examined the relative value of these measurements in comparison to ordinary clinical assessment using the Jones index in a study of the time course of onset of attacks of acute severe asthma observed concurrently both in general practice and in hospital in the Oxfordshire area. The relationship between the speed of onset of an attack of acute severe asthma and the apparent severity has also been studied.

Patients and Methods

This study was part of a prospective survey comparing attacks of acute asthma seen in hospital with those treated outside hospital by the general practitioner. The sole entry criterion was wheezing dyspnoea of sufficient severity to necessitate parenteral therapy from the attending doctor. Patients subsequently found to have left ventricular failure were withdrawn from the study. This definition was deliberately wide in order to include patients who might otherwise have been omitted, such as children with 'wheezy bronchitis' and adults with chronic bronchitis as well as asthma.

All cases of acute severe asthma ($n=184$) admitted to the central Oxford teaching hospitals (Churchill and John Radcliffe Hospitals) during a one-year period were entered into the study. In addition 34 general practitioners assisted with the study and entered the remaining cases ($n=77$). These general practitioners were based in 20 separate practices in the Oxfordshire region that had been selected to provide a balance between urban and rural communities.

At the time of presentation of a patient with an attack the attending doctor completed a simple form. This contained space for recording the measures of severity by the Jones index (Table I), peak expiratory flow rate, pulse rate and pulsus paradoxus, as well as the speed of onset of the attack. The point of onset of the attack was derived from the clinical history, and was the point when the patient first perceived that wheezing was worse than usual. The speed of onset was the interval between this point and the time at which the patient or his/her relatives sought emergency medical assistance. Further details were recorded when the patients were fully interviewed by the authors after recovery from the attack.

General practitioners were provided with peak flow meters and meters were readily available in hospital. No direct instructions were given to the doctors participating in the study to use these meters since we wished to observe the ways in which the study doctors chose to assess the asthma attacks.

Table I. The Jones index

Grade 1	Able to carry out housework, or job, with difficulty
Grade 2A	Confined to a chair or bed, but able to get up with moderate difficulty
Grade 2B	Confined to a chair or bed, but able to get up with great difficulty
Grade 3	Totally confined to a chair or bed
Grade 4	Moribund

RESULTS

Two hundred and sixty one consecutive episodes of acute severe asthma were studied in 232 patients (115 male, 117 female) and the age distribution of patients is shown in Table II. 190 (81.9%) of the patients were classified as 'extrinsic' asthmatics on the basis of at least one positive skin prick test or because of the onset of wheezing in childhood; the remaining 42 patients (18.1%) were classified as 'intrinsic' asthmatics. Of the adult patients, 20.5% were current smokers and 33.1% were previous smokers. Sputum production, sufficient to meet the MRC criteria for chronic bronchitis, was a feature in 26 patients.

The speed of onset of attacks is shown in Table III. Whilst 82 (31.7%) of the patients had been unwell for more than three days before presentation, 120 (46.3%) had developed symptoms in less than 24 hours. In 34 cases (13.1%) the speed of onset was extremely rapid and was less than one hour. The proportion with rapid-onset attacks (less than 24 hours speed of onset) was similar in male and female patients, but differed with the age of the patient (Table III). Rapid-onset attacks were more common in young patients and less common in the elderly ($\chi^2=66.27$; df$=16$; $P<0.001$), and occurred more often in 'extrinsic' asthmatics (Table III; $\chi^2=14.84$; df$=4$; $P<0.01$). Half the patients

(50.8%) reported previous attacks of acute severe asthma requiring parenteral therapy during the preceding year. The speed of onset of the index attack was not related to the frequency of these previous episodes.

The range of grades of severity of the episodes, using the Jones index, is shown in Table IV. 63 episodes (24.4%) were categorized in the two severest grades of attack, and 29 (46.8%) of these had a rapid speed of onset. The proportion having rapid attacks was similar in patients of all grades of severity. Further factors that did not influence the range of grades of severity were the age and sex of the patient, the frequency of previous episodes and the type of asthma (extrinsic or intrinsic).

Table II. Age distribution of patients

Age (years)	*No. of patients*
0–14	66 (28.4%)
15–29	57 (24.6%)
30–49	45 (19.4%)
59–60	48 (20.7%)
70+	16 (6.9%)

Table III. Speed of onset of episodes in differing age and diagnostic groups

	Speed of onset				
	<1 hour	<24 hours	1–3 days	3–7 days	>1 week
Age					
0–14 years	14	42	12	2	3
15–29 years	9	21	15	6	13
30–49 years	8	15	11	8	12
50–69 years	2	6	11	12	20
70+years	1	2	8	3	3
Type					
Intrinsic	3	6	13	10	10
Extrinsic	31	80	44	21	41
Total	34 (13.1%)	86 (33.2%)	57 (22.0%)	31 (12.0%)	51 (19..7%)

Two missing observations.

Peak expiratory flow rates on presentation were recorded in 160 episodes (Table V) with a mean of 23.1% of predicted values (SD 12.1%). PEFR did not correlate with the speed of onset of the attack, the sex of the patient or the type of asthma (extrinsic or intrinsic). A relationship was shown with age however ($r=0.29$; df$=158$; $P<0.001$), younger patients having higher percent predicted peak flow rates on presentation (Table V). When peak flow measurements were unrecordable, because of the severity of the attack, minimum values (60 litres/minute) were allocated. In a further 101 episodes

(38.7%) peak flow meters were not used. The proportion of childhood attacks in which meters were not used (69.9%) exceeded the proportion of adult attacks (26.6%). Failure to record peak flow readings was not related to the grade of severity of the attack.

Pulse rates on presentation were measured in 250 episodes, with a mean of 118.4/minute (SD 22.9). Children had higher pulse rates on presentation (mean 132.8/minute; SD 25.2), but otherwise there was no correlation with age. The degree of tachycardia did not correlate with the speed of onset of the attack. Pulsus paradoxus was noted to be present in 95 episodes (36.4%).

Table IV. Relationship between severity of episodes (Jones index) and speed of onset

Speed of onset	*Jones index*				
	1	2A	2B	3	4
<1 hour	3	10	9	6	6
<24 hours	9	23	36	16	1
1–3 days	6	21	18	11	0
3–7 days	1	11	10	8	1
>1 week	3	16	19	7	6
Total	22 (8.5%)	81 (31.4%)	92 (35.7%)	48 (18.6%)	15 (5.8%)

Three missing observations.

Table V. Peak expiratory flow rate (PEFR) measurements on presentation, according to age of the patient

Age (years)	*Presentation PEFR* (% predicted ± SD)	*No. of patients*
0–14	30.5±10.5	22
15–29	24.1±15.3	44
30–49	21.4± 8.9	44
50–69	21.1±11.0	40
70+	18.3± 8.2	10
Total	23.1±12.1	160

A comparison of the different measures of severity is shown in Table VI. There is a trend for the patients with the severest attack, judged by the Jones index, to have the lowest peak flow rates and the most marked tachycardia. Statistically significant correlation coefficients were found between several of the measures of severity, but with relatively low values. Both peak expiratory flow rate and pulse rate correlated well with subjective clinical assessment using the Jones index, but much less well with each other.

None of the severe asthma attacks were fatal. Five patients required ventilation (IPPV) on arrival at hospital and then recovered. One of these five patients had a rapid speed of onset attack following a β-blocker tablet and is reported elsewhere (Raine et al. 1981). The remaining four patients that required ventilation had a slower evolution of the attack, but three deteriorated rapidly and were rushed into casualty without having time to contact a general practitioner.

Differences were found in several respects between patients managed at home by the general practioner and those managed in hospital. These and the patterns of drug therapy will be discussed in a separate report.

Table VI. Relationship between different measures of severity in the total group of patients

Grade (Jones index)	*Initial PEFR* (% pred.; mean ± SD)	*Initial pulse rate (adults)* (/min; mean ± SD)	*Pulse rate (children)* (/min; mean ± SD)
1	36.1±9.8	106.0±20.9	114.8±21.6
2A	28.7±12	108.5±16.3	123.8±22.4
2B	22.8±15.6	111.6±19.7	139.9±21.7
3	15.6±4.9	119.6±19.7	157.8±25.8
4	14.4±4.6	132.3±21.1	140.0±14.1
Comparison of measures of severity	*No.*	*r*	*P*
Jones index *v* PEFR	160	−0.4357	<0.001
Jones index *v* pulse rate	181	0.5433 (adults)	<0.001
	66	0.5571 (children)	<0.001
Jones index *v* paradox	95	0.2569	<0.001
PEFR *v* pulse rate (adults)	130	−0.1925	<0.05

DISCUSSION

It is clear that whereas some severe asthmatic attacks develop over several days, others develop extremely rapidly. This study attempts to define the relative frequency of these two types of attack since there is no agreement on this point. Most surveys of deaths in acute asthma have found the attack to be short. Two surveys found that there was less than a 24-hour history before death in 70.6% (Speizer et al. 1968) and 66% (Ormerod & Stableforth 1980) of cases. Another survey of asthma deaths found that only 18.5% of attacks had such a short length of history (Macdonald et al. 1976*b*). If the two Cardiff surveys (Macdonald et al. 1976*a* and *b*) are combined then 54% of cases were of rapid onset (<24 hours). A survey of non-fatal attacks showed that 39% of admissions had less than a 24-hour history (Cooke et al. 1979), but was from a unit with an emergency admission service. Bellamy and Collins (1979) showed poorly controlled wheezing for a mean period of five weeks before presentation in a small group of 44 patients, but three of their seven severest cases (Grade 3 or 4) had suddenly deteriorated within 24 hours. Other investigators suggested that the majority of life-threatening attacks evolved over days or even weeks (Davis et al. 1980). They conceded that a minority of cases developed rapidly, but gave no figures.

The management of acute severe asthma depends on which of these two views is correct. If the attacks evolve slowly it is safe to concentrate resources on improved management in the home by the patient and general practioner. If a significant proportion of attacks evolve rapidly then this policy is inadequate and an emergency admission facility becomes more appropriate. Our results show that in 46% (120 cases) of acute severe asthma attacks the speed of onset was less than 24 hours and that in 13% (34 cases) it was less than one hour. Patients in our study were at least as ill as those in other studies, but in any case the proportion having rapid attacks is independent of severity of the attack by all parameters that we recorded.

The difficulties of recognizing the severity of an asthma attack are well recognized, and poor assessment has often been described in association with asthma deaths (Cochrane & Clark 1975; Ormerod & Stableforth 1980). An index that graded patients according to function was introduced by Jones in 1971 (Table I). Even Grades 1 and 2 of this index may indicate quite severe asthma (Clark 1977). Grades 3 and 4 are life-threatening (Davis et al. 1980) and hospital admission has been recommended for Grades 2A and above (Jones). Recently the emphasis has been on objective rather than subjective measures of severity, and the degree of tachycardia was found to be useful by Cooke et al. (1979). As they reported we also found pulse rates to be higher in young patients but had no further evidence to support the claim that these younger patients were more ill.

Pulsus paradoxus is often present in acute severe asthma and has been shown to have a quantitative relationship to reductions in FEV_1 in a small group of patients (Knowles & Clark 1973). The sign was recorded in 36% of our episodes but may have been more frequent since its absence was often not recorded. When measured there was a poor correlation with other measures of severity.

Surveys investigating the circumstances of asthma deaths have mentioned the under-usage of measures of airflow obstruction (Ormerod & Stableforth 1980) and widespread use of peak flow meters has been recommended (Seaton 1978). We found that a large proportion of adult patients were tested with a peak flow meter. Correlations between peak flow readings and other measures of severity were disappointingly low.

There are interesting parallels between our findings and a recent study of recovery from acute severe asthma attacks (Smith 1981). He describes different patterns of recovery, each with a different speed. We feel that the same applies to the speed of onset of the asthma attack and suggest that the proportion having rapid attacks is sufficiently high to warrant special treatment such as a direct emergency admission service. Smith comments that recovery seems to be more rapid in younger patients and we suspect that the speed of onset of the attack is also more rapid in the younger patient. Anderson et al. (1980) have found an increasing rate of childhood asthma admissions in an area of London, with a particular increase in self-referrals. If children commonly have rapid attacks this might be considered appropriate. The study by Smith also seemed to confirm our finding that elderly patients had lower peak flow rates on presentation, although we did not find the elderly to be more ill by other criteria.

Criticisms of poor assessment of the severity of asthma attacks have been made, but what measures of severity should we advocate as being helpful? There is no absolute yardstick against which we can compare any individual measure of severity, but we can compare one with another. The study by Smith (1981) included arterial blood gas analysis but found no correlation greater than 0.5 between any two measures. We found several significant correlations, but none higher than 0.55, which confirms the weakness of any factor taken in isolation. All of our higher correlations included the subjective clinical assessment by the Jones index. Clinical assessment of a patient with acute severe asthma must therefore embrace as many objective measures of severity as is possible, but must also include a simple subjective clinical assessment based on function of the patient.

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DIAPHRAGMATIC BREATHING TRAINING AND WALKING PERFORMANCE IN CHRONIC AIRWAYS OBSTRUCTION

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Summary

Eight patients with chronic obstructive bronchitis and moderate disability entered a pilot study of the effects of controlled diaphragmatic breathing. They received three weeks of placebo physiotherapy (shoulder exercises) followed by three weeks of instruction on controlled diaphragmatic breathing. No beneficial effects were observed on exercise performance or the perceived strain of exercise.

INTRODUCTION

Accepted physical methods for helping patients with chronic airways obstruction include exercise training (Cockroft et al. 1980) and measures to aid the removal of sputum. 'Breathing exercises' are widely prescribed and practised but their effects on exercise performance have never to our knowledge been assessed. Objective evaluation of physical treatment in chronic lung disease has recently been called for (Committee on Thoracic Medicine 1981). The stated aims of breathing exercises are to make more efficient use of the lungs by improving the method of breathing and to enable the patient to control his breathing during attacks of breathlessness. 'Diaphragmatic breathing' is an important component of such breathing exercises, the rationale of which appears to be to improve ventilation to the bases of the lungs and reduce ineffectual movements of the upper rib cage. If effective, the instructions should either improve exercise performance or reduce the strain of exercise, or both. We carried out a pilot study to test this hypothesis.

Materials and Methods

Patients with stable chronic airways obstruction were studied. All had exercise performance limited by breathlessness of at least grade II on the MRC scale (Fletcher et al. 1959). Laboratory tests were carried out on three occasions at intervals of three weeks and at approximately the same time of day. The test consisted of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and a 12-minute walking test (12 MD) (McGavin et al. 1976), before and after inhalation of 200 μg of salbutamol aerosol. The strain experienced during the exercise test was assessed by Borg's rating of perceived exertion (RPE) (Borg 1970).

After the first visit patients underwent a three-week course of placebo exercises. They attended the physiotherapy department thrice weekly and carried out 35 minutes of rope and pulley shoulder exercises. The laboratory tests were repeated and the patients then underwent a three-week instruction course of diaphragmatic breathing and breathing control exercises. These were essentially as described by Gaskell (1980) to encourage movement of the lower chest and abdomen.

One of us (C.M.S.) gave instruction initially at rest but then supervised the patients during increasing activity, checking during exercise that they were breathing as instructed. The patients were asked to practise these exercises at home. They were advised to avoid exercise dyspnoea by adjusting the rate of exercise but were asked to keep the level of their general activities constant during the trial. The diaphragmatic breathing exercises were checked by thrice weekly attendances in the physiotherapy department and again before the final laboratory test.

The results were analysed by the t test for paired observations.

RESULTS

The group consisted of eight patients (six male) with a mean age (±SD) of 67±6 years. The mean FEV$_1$/FVC ratio was 34±8%. The mean values for FEV$_1$, FVC, 12 MD and RPE, before and after placebo (shoulder exercise) therapy and after active (diaphragmatic breathing) therapy, are given in Table I. The changes in spirometry and walking performance are expressed as percentage difference from the previous test; change in RPE has been expressed in absolute terms. The results of the paired t-test are also shown. No significant changes were recorded in any measurement at any stage.

Table I. Mean values (±SD) of FEV$_1$, FVC, 12-MD and RPE before and after placebo therapy and after active therapy

	Initial	*After shoulder exercises*	*t*	*After diaphragmatic breathing*	*t*
FEV$_1$ (ml)	950±270	940±290	−0.37	900±270	−1.69
FVC (ml)	2790±610	2850±580	0.86	2900±510	2.1
12-MD	936±82	928±111	−0.25	945±145	1.62
RPE	10.7±1.6	11.2±2.3	0	10.6±2.7	−1.96

The t-values are obtained by comparing percentage changes from the previous test in the case of FEV$_1$, FVC and 12-MD and absolute changes in the case of RPE.

DISCUSSION

The design of this study was suboptimal in that it was a single-blind and there was no randomization of order. The technician would therefore be aware of the treatment and there may have been a systematic change in the placebo effect. This design was adopted because the persistence of any benefit from active physiotherapy was unknown; indeed the benefit might have been permanent.

The exercises were intended to make more efficient use of the lungs by diaphragmatic movement and to enable the patient to control his breathlesssness during exercise. If effective they should either have enabled the patient to walk further or have reduced the strain of exercise. However, no change either in walking distance or in perceived strain of exercise was observed. Borg's scale of rating of perceived exertion has been investigated by several groups of workers and the score has been found to correlate with physiological indicators of physical stress during exercise (Edwards et al. 1972).

We have found no indication that patients with airways obstruction and a 12-minute walking distance of around 930 m benefit from diaphragmatic breathing exercises.

Furthermore there is no trend suggesting that some patients walked as far for less perceived stress while others walked faster for the same amount of stress. It is possible, however, that more disabled patients might derive some benefit.

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COMPARISON OF PEAK EXPIRATORY FLOW RATE AND FORCED EXPIRATORY VOLUME IN ONE SECOND IN HISTAMINE CHALLENGE STUDIES IN CHILDREN

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Summary

The difficulty in performing FEV_1 in young children prompted us to assess whether PEFR could be used to measure the response to inhaled histamine. In 123 children with recurrent respiratory symptoms we found a highly significant correlation ($r = 0.83$, $P < 0.001$) between the percentage fall from base-line of FEV_1 and PEFR. We also performed histamine challenge tests using PEFR alone on 56 children too young to manage spirometry and found our procedure reliable. PEFR is an adequate measurement in histamine provocation studies and can be used interchangeably with FEV_1. The criterion for a positive test is a 20% fall in either PEFR or FEV_1.

INTRODUCTION

Histamine provocation testing is a well established method of assessing bronchial reactivity and sensitivity (Mellis et al. 1978). When Chai et al. (1975) standardized inhalation challenge techniques, their criterion for a positive test was a 20% fall from base-line of forced expiratory volume in one second (FEV_1). However, many young children have difficulty with spirometry and this is particularly likely when repeated procedures are required to establish a dose–response curve for histamine. On the other hand, peak expiratory flow rate (PEFR) is a simpler technique for young children to master (Waring 1972/3). We have compared FEV_1 and PEFR in histamine challenge tests to determine whether PEFR alone is a reliable criterion.

Materials and Methods

We studied a total of 179 patients, whom we divided into two groups. The first group comprised 123 children able to perform spirometry reliably. There were 51 females and 72 males whose ages ranged from 4.2 to 17.4 years (mean 8.1 years). The second group contained 56 children who were too young to perform spirometry reliably but who could use a peak flow meter. 21 were females and 35 were males and their age range was 3.8–7.3 years (mean 5.4 years). Both groups had lower respiratory tract symptoms such as chronic cough or recurrent bronchitis. They were referred for histamine challenge testing to assess bronchial reactivity and possible benefit from bronchodilator therapy. No subjects were wheezing at the start of the study, none was on antihistamines and none had received bronchodilators within four hours of the challenge.

We used the standardized histamine challenge described by Chai et al. (1975). The following concentrations of histamine were used: 0.5, 1.0, 2.5, 5.0 and 10.0 mg/ml. We did not use the lower concentrations of histamine as originally suggested by Chai et al. (1975). By eliminating these low concentrations the number of measurements is reduced and young children are more liable to complete the test reliably. No child in this study was so sensitive to histamine that his safety was compromised by starting at 0.5 mg/ml of histamine. Each patient commenced with diluent only (phenol-buffered saline) and progressed stepwise to the maximum concentration unless a positive response was observed. Each child took five successive slow inspiratory capacity breaths of each concentration through his mouth. The aerosol was administered via a Bennett twin jet nebulizer using a Hudson face mask and an air flow of 8 litres/minute. Three minutes after each concentration of histamine was administered several peak expiratory flow measurements were made with a Wright peak flow meter (standard or low range model as appropriate) followed by several forced vital capacity manoeuvres on a Godart water-sealed spirometer. The best readings were used to calculate the changes in PEFR and FEV_1 from the prechallenge measurements. A positive response to histamine was taken as a 20% or greater decrease in FEV_1 compared with the pre-challenge value. When this occurred, the study was ceased and a bronchodilator aerosol administered. In addition, we auscultated the chest for the presence of expiratory rhonchi or wheeze before commencing the challenge and after each concentration of histamine.

The 56 children who were unable to perform forced vital capacity manoeuvres used the peak flow meter alone. In this group a positive response to histamine was taken as a 20% or greater decrease in PEFR compared with the pre-challenge value. Again, we auscultated the chest regularly for clinical evidence of airways obstruction.

Table I. Bronchial sensitivity to histamine

Result		*No.*
Negative		51
Positive		72
at 2.5 mg/ml	9	
at 5.0 mg/ml	26	
at 10.0 mg/ml	37	
Total		123

RESULTS

In the group of 123 subjects, two were studied twice and a further two were excluded from analysis. We excluded a 12-year-old boy who developed a hoarse voice at 10 mg/ml of histamine. Although FEV_1 remained unchanged, PEFR fell by 34% and both his hoarse voice and PEFR did not reverse with bronchodilators. He was presumed to have developed laryngeal oedema (Douglas 1975). In addition, a four-year-old boy whose technique initially enabled FEV_1 to be measured was unable to perform a forced vital capacity when he developed an audible wheeze. He was able to use a peak flow meter and PEFR fell by 46%.

Of the remaining 123 studies analysed, 72 showed a 20% or greater fall in FEV_1. Table I indicates the dose of histamine needed to produce this fall. There was a highly significant correlation ($r = 0.83$, $P < 0.001$) between the falls in FEV_1 and PEFR (Fig. 1). Five patients had a 20% or greater fall in FEV_1 *without* a 20% fall in PEFR, while seven patients had a 20% or greater fall in PEFR *without* a 20% fall in FEV$_1$. In 11 of these 12 subjects, the 20% fall in FEV$_1$ or PEFR occurred at the maximum concentration of histamine (10 mg/ml).

In the second group of 56 children who performed PEFR alone 36 showed a 20% or greater fall in PEFR. One boy lost his voice and was excluded from further analysis. Thirteen of the remaining 35 tests were positive at a histamine concentration of 5 mg/ml or less and the average fall in PEFR for the 35 tests was 34%. Three of the 20 negative studies were thought to be false-negatives because we heard an audible wheeze or expiratory rhonchi during the challenge.

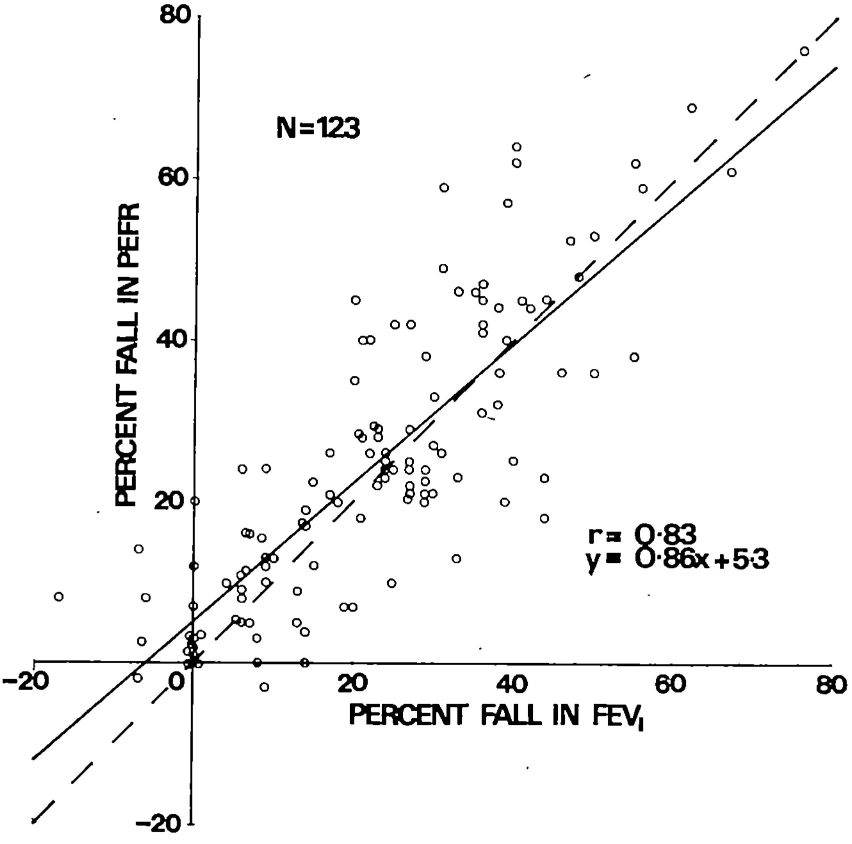

Fig. 1. Relationship between percentage fall in FEV$_1$ and percentage fall in PEFR for patients with lower respiratory tract symptoms. Dashed line is line of identity, unbroken line is regression line

Discussion

The main finding in our study was the good correlation between FEV$_1$ and PEFR in histamine provocation tests in children. A smaller study in adult asthmatics (Shoeffel et al. 1980) supports our conclusion that a 20% or greater fall in PEFR may be used instead of FEV$_1$ in histamine challenge testing.

In the large group of 123 children, 12 had a positive challenge by one of the measurements (FEV_1 or PEFR) but a negative challenge by the other. With one exception, the conflicting result occurred at 10 mg/ml of histamine. Four of these conflicting results were marginally positive by one test, with a fall in FEV_1 or PEFR of between 20% and 22%, but marginally negative by the other, with a fall in FEV_1 or PEFR of more than 15% but less than 20%. Furthermore, we have demonstrated that it is possible to obtain meaningful histamine challenge results in a group of 56 young children using only PEFR. Testing these children has obvious limitations but we believe our methodology is adequate.

Many children have recurrent lower respiratory tract symptoms which may be on an asthmatic basis. The detection of abnormal bronchial reactivity in this group is important from a therapeutic viewpoint, enabling bronchodilator therapy to be used on a more rational basis. PEFR is an adequate measurement in histamine provocation studies and the criterion for a positive test is a 20% fall in PEFR.

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DO ORAL AND INHALED TERBUTALINE HAVE DIFFERENT EFFECTS ON THE LUNG?

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Summary

The effect of inhaled or oral terbutaline on the subsequent response to inhaled terbutaline was studied using a double-blind cross-over technique in 12 asthmatic patients. 12 indices of respiratory function were obtained from the maximal flow-volume loop and a single-breath inert gas technique. These were used to evaluate the effect and to attempt to distinguish the site of action of the drug. Although the initial dose of inhaled terbutaline had a greater immediate effect than its oral counterpart there were no significant differences in the response to subsequently inhaled terbutaline. These findings do not support recent suggestions that oral administration has a greater effect on distal airways or promotes the effects of inhaled bronchodilators.

INTRODUCTION

There is still debate as to the size of airway which is most affected in asthma and, as a corollary, whether therapy specifically aimed at dilating the distal airways is beneficial. Bloomfield et al. (1979) compared intravenous and inhaled salbutamol in severe asthmatics and demonstrated equal bronchodilator action. Spiro et al. (1975) and Pierce et al. (1981) made similar observations in patients with moderately severe asthma, using salbutamol and terbutaline respectively. However, Svedmyr and Svedmyr (1979) and Larsson and Svedmyr (1977) have suggested that oral therapy has a greater effect on airways in the periphery of the lung and it has been argued that this might amplify the effect of inhaled treatment; this suggests that combining both routes may be of advantage. To investigate this we compared the effect of pretreatment with either oral or inhaled terbutaline on subsequent inhalations of the same drug, looking at 12 indices of lung function. These measurements were chosen in an attempt to distinguish between central and peripheral function.

Material and Methods

Patients

We studied eight men and four women (mean age 44, range 25–63) with stable long-standing asthma and a demonstrable increase in FEV_1 of 25% following inhaled bronchodilators. Three were active smokers, three had stopped smoking for more than four years and six had never

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smoked. All had abstained from beta-2 stimulants and disodium cromoglycate for eight hours and from methylxanthine for 12 hours. Patients continued their maintenance dose of oral or inhaled steroids during the trial.

Lung function tests

Maximal flow volume loops were obtained using a dry rolling-seal spirometer (Ohio 840). The volume signal was differentiated to give flow and the flow–volume loops constructed and plotted by computer (Prime 300). Forced expiratory volume in one second (FEV_1), forced expiratory volume in three seconds (FEV_3), forced vital capacity (FVC), peak expiratory flow rate (PEFR), maximal expiratory flow rates at 75%, 50% and 25% of vital capacity above residual volume (MEF_{75}, MEF_{50} and MEF_{25}) and peak inspiratory flow rate (PIFR) were measured for these loops.

Single-breath argon freon tests (Denison et al. 1980*a*, *b*) were performed with the patient seated upright and at rest. From residual volume the subject inhaled a known volume of the test gas (10% argon, 4% freon, 35% oxygen and a balance of N_2), held his breath for one or two seconds and then exhaled slowly and evenly back to residual volume. The changing partial pressures of argon and freon were monitored at the lips by a respiratory mass spectrometer (MGA 200, Centronics Ltd) and exhaled volumes were determined with water-filled spirometer. These variables were plotted against time, on a flat bed recorder. The accessible gas volume (VA′) and effective pulmonary blood flow ($\dot{Q}p$) were calculated by the method developed by Denison et al. (1980*a*) and the 'slopes of phase 3' were determined from the fall in argon concentration signal between 750 ml and 1250 ml of expired volume, expressed as a percentage of the original argon signal.

Protocol

Each patient was studied under double-blind cross-over conditions on two consecutive mornings. Base-line measurements of six maximal flow–volume loops, five argon/freon tests, radial pulse and blood pressure were taken. On one morning they then received two inhalations of 0.25 mg terbutaline plus a placebo tablet and on the other a 2.5 mg terbutaline tablet plus two placebo inhalations. The measurements were repeated at 60, 90 and 120 minutes after the initial dose. After the 120-minute observations the patients received two inhalations of 0.25 mg of terbutaline and recordings were made 30 minutes later. A further two inhalations of terbutaline were then given and all recordings repeated 30 minutes later.

Analysis

For each set of data the best index of each flow–volume loop variable was selected and the average values for the slope of phase 3, accessible lung volume and pulmonary blood flow calculated. All results were then expressed as a ratio of that obtained at time zero and compared between treatment days using a paired *t*-test.

RESULTS

Absolute values for all variables under base-line conditions were not significantly different from day 1 to day 2. The effect of treatment on the spirometric observations are shown in Figs 1 and 2. These figures demonstrate that inhaled terbutaline produced a rapid increase in all variables at 60 minutes, with a subsequent small decline at 90 and 120 minutes. Oral terbutaline resulted in a gradual progressive rise in FEV_1, FEV_3, FVC, PEFR and MEF_{75} but no significant response in MEF_{50} and MEF_{25}. At 120 minutes, however, there was no significant difference between the two days. Subsequent inhalations of terbutaline resulted again in a rapid increase in all variables but no significant differences between days.

The values for the slope of phase 3, accessible gas volume (VA′) and accessible residual volume demonstrate a similar pattern to the flow volume data (Fig. 3a–c), although there is still a significantly greater decrease in residual volume and slope of phase 3 following inhaled terbutaline at 120 minutes. Effective pulmonary blood flow, however (Fig. 3d), demonstrated a different pattern. Both oral and inhaled terbutaline produced a significant increase in effective pulmonary blood flow ($\dot{Q}p$) after 60 minutes. This increase was maintained up to 120 minutes following oral terbutaline, but $\dot{Q}p$ had returned to baseline values by 120 minutes following inhaled terbutaline. Subsequent inhalations of terbutaline produced significant further increases in $\dot{Q}p$ on both days but the overall increase in $\dot{Q}p$ was greater when oral terbutaline was the initial treatment.

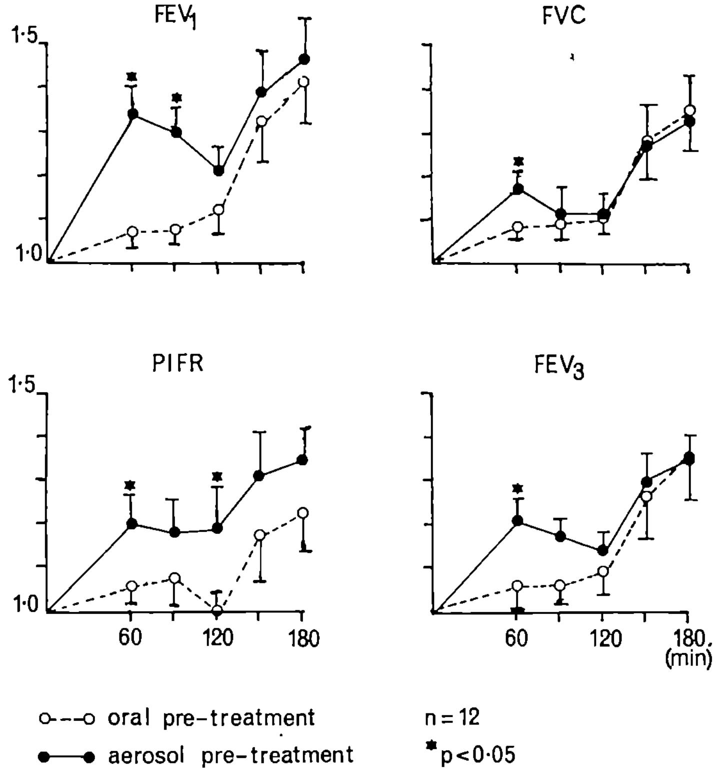

Fig. 1. Group means (±SEM) of FEV_1, FVC, PIFR and FEV_3 expressed as a ratio of base-line values against time. Initial therapy given after time zero and subsequently inhalations immediately after 120 and 150 minutes

DISCUSSION

In this study inhaled terbutaline resulted in a rapid and significant increase in all spirometric variables (Figs 1, 2). This was equally true of those indices (FVE, FEV_3, MEF_{50} and MEF_{75}) believed to be predominantly affected by peripheral airways function as of those variables (FEV_1, PIFR, PEFR, MEF_{75}) thought to be affected by the central airways. Oral terbutaline, on the other hand, resulted in a gradual increase in spirometric variables but these increases were again similar in those variables (PEFR, MEF_{75}, FEV_1) reflecting central airways function and those reflecting peripheral airways function (FVC, FEV_3, FEF_{50}). Inhaled terbutaline (Fig. 3a–c) also resulted in a decreased slope of phase 3, reduced residual volume and increased accessible lung volume. This again suggests a peripheral effect of inhaled terbutaline. Several studies support this evidence for peripheral actions of inhaled bronchodilators. Benatar and König (1974) demonstrated that salbutamol rapidly reversed the residual volume changes in exercise induced asthma, and Antic and Macklem (1976) also showed that inhaled salbutamol reversed expiratory flow limitation in small airways. Wagner et al. (1978) showed that inhaled bronchodilators can rapidly affect $V/\dot{Q}$ ratios and arterial blood gases.

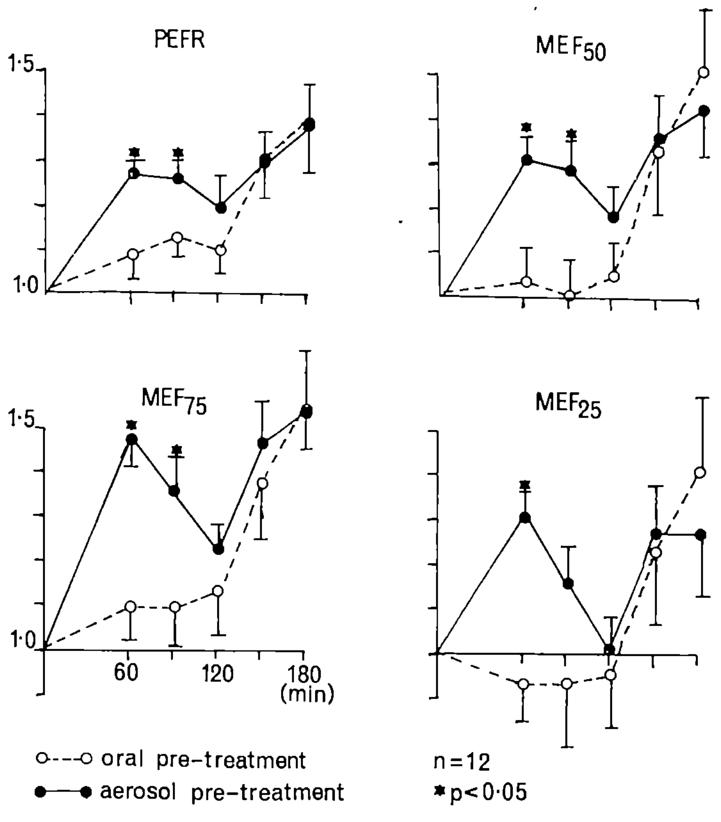

Fig. 2. The same plots as Fig. 1 for PEFR, MEF_{75}, MEF_{50} and MEF_{25}

The values obtained for effective pulmonary blood flow ($\dot{Q}p$) by the single breath test are a measure of that part of the cardiac output which comes into contact with ventilated lung. They are therefore dependent upon absolute cardiac output, accessible lung volume and $V/\dot{Q}$ matching. The increase $\dot{Q}p$ at 60 minutes (Fig. 3d) following inhaled terbutaline was associated with improved gas mixing (decreased slope to phase 3 and increased accessible lung volume) and probably reflects improved $V/\dot{Q}$ matching.

However, the significant increase in effective pulmonary blood flow following oral terbutaline at 60 minutes cannot be explained by this mechanism because of the lack of an associated improvement in gas mixing. This latter increase probably reflects an increase in cardiac output due to the systemic effects of the absorbed terbutaline.

In this study the doses of oral and inhaled terbutaline selected resulted in an equal degree of bronchodilation at 120 minutes regardless of the spirometric variable chosen (excepting PIFR). Further inhalations of terbutaline given at this stage resulted in significant and equal increases in all spirometric variables on both days. Thus the route of administration of the initial terbutaline did not affect the bronchodilator action of subsequently inhaled terbutaline. This study fails to confirm the observation of Svedmyr and Svedmyr (1977) that predosing with oral bronchodilators results in a greater bronchodilator effect by subsequently inhaled bronchodilators.

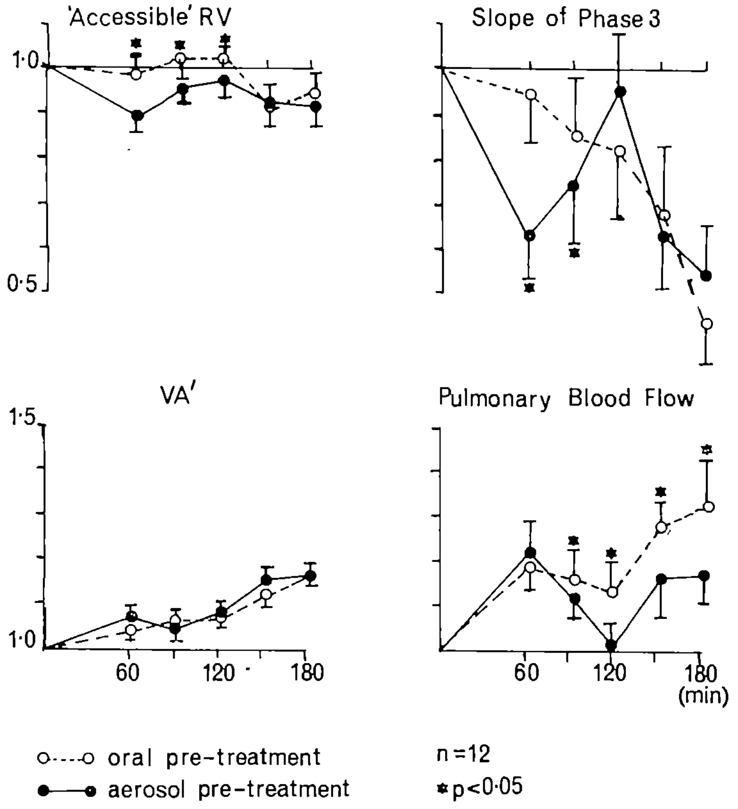

Fig. 3. The same plots as Fig. 1 for accessible residual volume (VA′ – inhaled volume), accessible gas volume (VA′), slope of phase 3 and pulmonary blood flow.

We conclude that oral and inhaled terbutaline have similar effects on central and peripheral airways and differ only in their speed of action. There is no evidence to suggest that predosing with oral bronchodilators will result in any greater subsequent response to inhaled bronchodilator.

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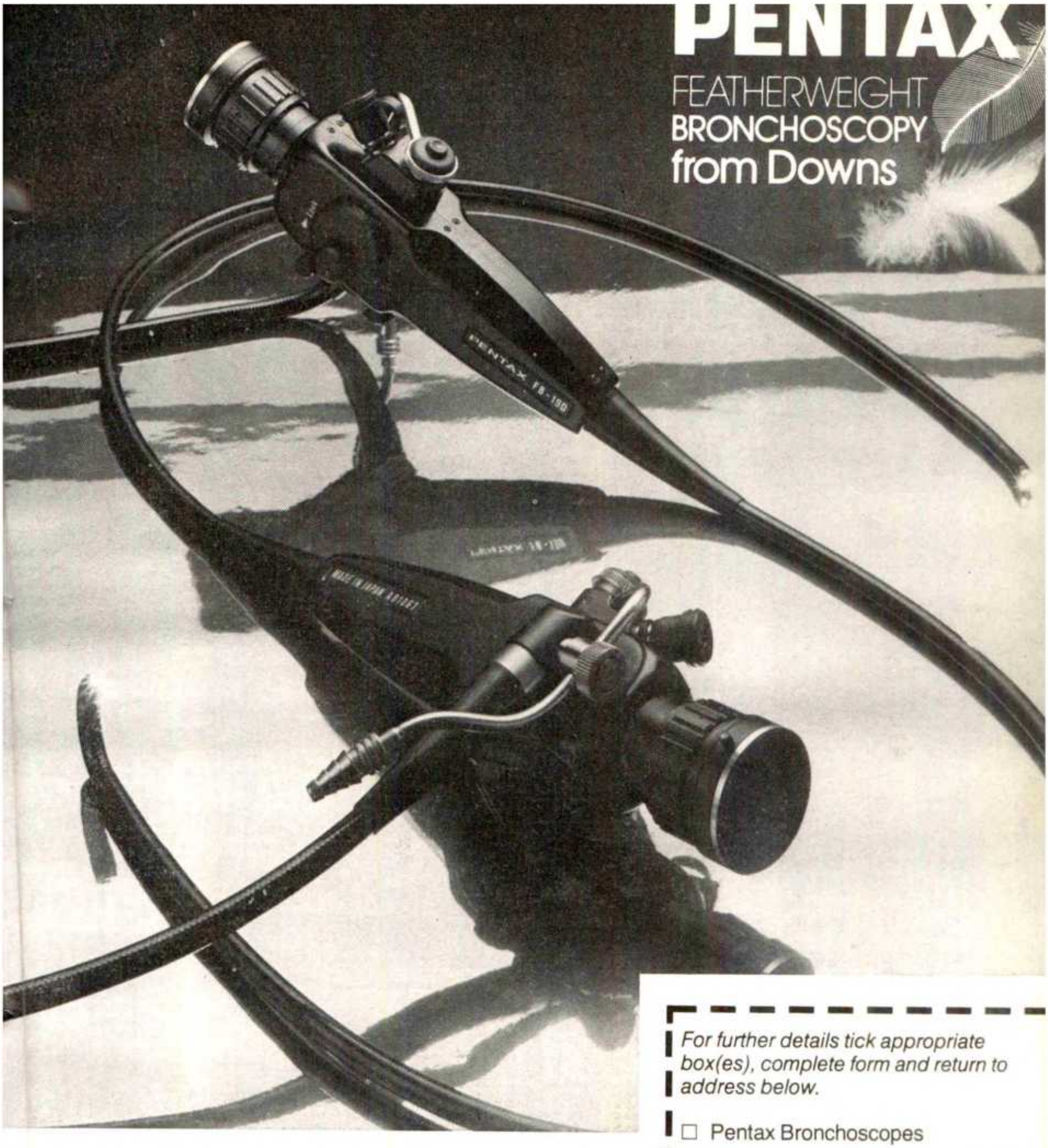

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Br. J. Dis. Chest (1982) *76*, 177

CONGENITAL LOBAR EMPHYSEMA: A CASE WITH BRONCHIAL ATRESIA AND ABNORMAL BRONCHIAL CARTILAGES

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Summary

An infant with congenital left upper lobe emphysema presenting with respiratory distress and failure to thrive, which necessitated lobectomy, is described. Careful pathological examination revealed two defects in association with the emphysema: bronchial atresia and defective bronchial cartilage in the affected lobe. Whilst congenital lobar emphysema is the term usually employed to describe this clinical presentation of respiratory distress in infancy, 'panlobular emphysema of infancy' would be a more accurate description. Congenital defects in the airways may account for the development of emphysema, but there may be a more fundamental congenital tissue abnormality at alveolar level.

INTRODUCTION

Congenital lobar emphysema is a clearly recognized clinical type of respiratory distress in early infancy. The radiographic appearances are of marked over-distension, usually of an upper lobe, with compression of the remaining normal lung, mediastinal shift and herniation of the over-inflated lung through the anterior mediastinum. There is a relative uniformity of clinical presentation, with the vast majority requiring early surgical intervention because of severe respiratory embarassment (Taber et al. 1974). Despite the consequent availability of lung tissue for histopathological study precise understanding of the mechanisms involved in the development of the condition is still lacking.

This report describes an infant with congenital lobar emphysema which was treated surgically. The emphysema was confirmed pathologically and was associated with both bronchial atresia and defective bronchial cartilages.

Case Report

A 10-week-old first child of healthy, unrelated parents was admitted for investigation of breathlessness and failure to thrive. The pregnancy had been uneventful with a full-term caesarean section delivery of a 3.5 kg female infant. She had persistent tachypnoea from birth and because the radiographic appearance of dextrocardia suggested congenital heart disease, she was digitalized. This failed to influence her symptoms.

Examination revealed a thin tachypnoeic infant. There was a hyperresonant percussion note over the left chest and breath sounds on the left were decreased. The apex beat was palpable over the right chest, but the cardiovascular system was otherwise clinically normal. The chest radiograph showed marked over-expansion of the left upper lobe with compression of the left lower lobe and right lung (Fig. 1). The heart was in the right hemithorax but there was a left-sided aorta and situs solitus. The arterial blood gases in air revealed mild hypoxia and hypocapnia ($P\text{O}_2$ 10.46 kPa; $P\text{CO}_2$ 4.06 kPa). An isotope lung scan demonstrated no ventilation or perfusion of the left upper lobe, but normal ventilation and perfusion in the left lower lobe and right lung.

Following the diagnosis of left upper lobe congenital emphysema a thoracotomy was performed when she was 15 weeks of age. A grossly over-inflated left upper lobe was resected. Postoperatively the left lower lobe was rather slow to expand and in spite of the resection the heart remained in the right hemithorax. Nevertheless, on discharge 10 days later she was feeding well and gaining weight; her respiration rate had diminished to 40/min. At six months of age she still had dextrocardia and there was marked pectus excavatum. She had no respiratory distress and was developmentally normal and thriving. The chest radiograph showed the left lower lobe occupying most of the left hemithorax and persistent dextrocardia (Fig. 2).

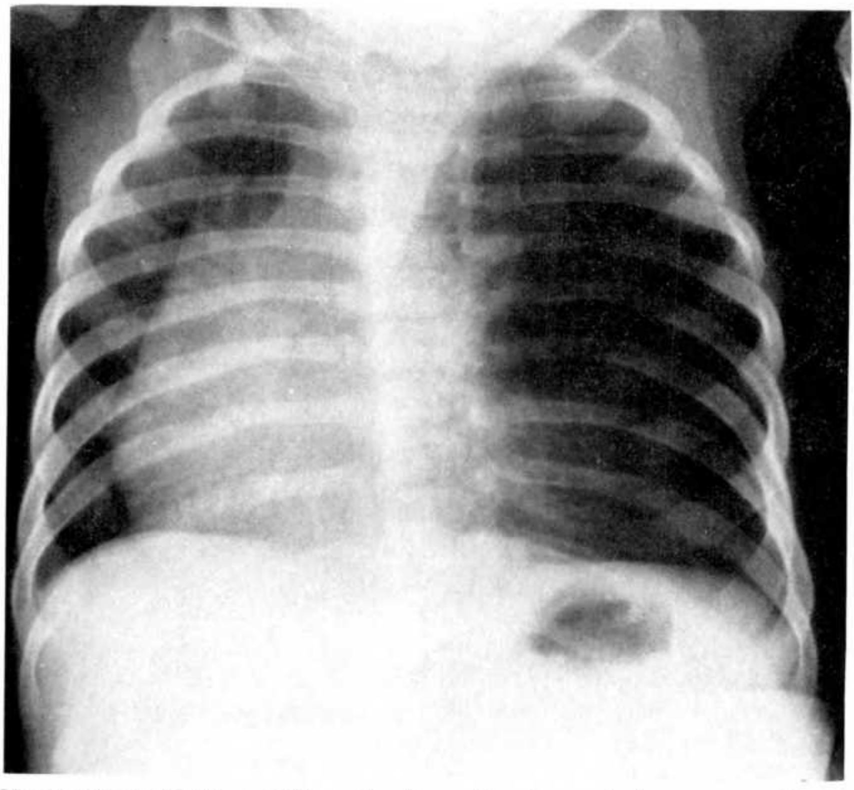

Fig. 1. Chest radiograph taken at 10 weeks of age showing marked over-expansion of the left upper lobe and dextrocardia with left-sided aorta and situs solitus

PATHOLOGY

A small part of the specimen was sampled for electron microscopy and the remainder was distended lightly with 10% formol saline solution and immersed in this for seven days. The external surface was smooth and free of adhesions. Parts of the parenchyma were pale and soft as though previously over-distended. The bronchi supplying the apical, anterior and both lingular segments were probe-patent. The bronchus to the posterior segment showed atresia proximally; it could not be probed from the hilar end but was widely patent distal to the obstruction.

Samples of several bronchi were dissected from the specimen and the cartilage stained with acidic toluidine blue, dehydrated through graded alcohols and cleared in methyl salicylate (Stovin 1959). The resulting preparations showed a partial deficiency of cartilage in the bronchus to the apical segment and the cartilages of the bronchus to the posterior segment appeared more widely separated than normally. The cartilages of the bronchi to the anterior and upper lingular segments appeared normal (Fig. 3).

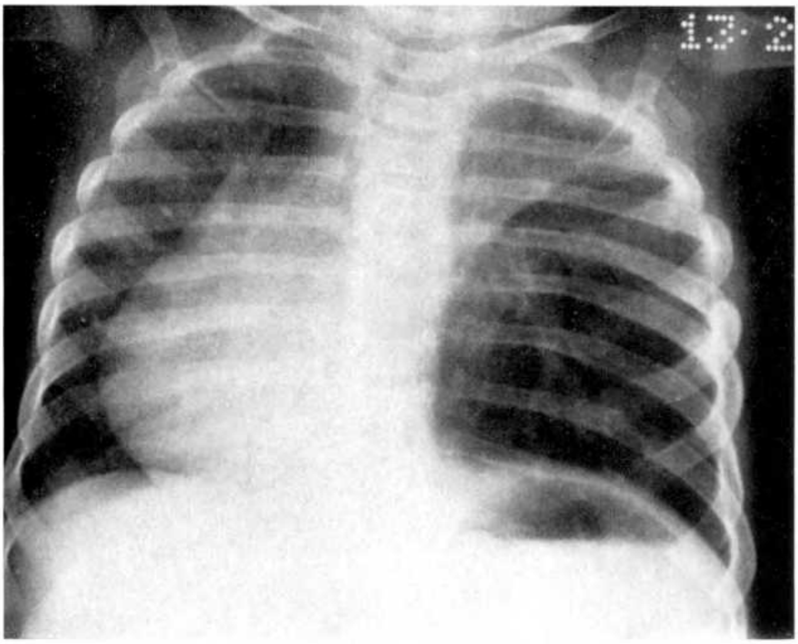

Fig. 2. Chest radiograph taken at six months of age showing persistent dextrocardia and the left lower lobe filling most of the left hemithorax

Histological sections of the site of atresia showed an old scar composed of broad bands of collagen fibres (staining by Van Gieson's method), with a small number of fibroblasts scattered between them. Sections of lung tissue showed emphysema, particularly in the posterior segment (Fig. 4). The alveoli appeared distended and their walls thinned. There was a reduction in the number of alveolar walls as judged by comparison with control material, as well as distension of the delicate lung parenchyma. The destruction was graded as mild, and was mostly evident in walls projecting towards alveolar ducts. Detailed quantitative studies of the alveoli could not be applied because the lung had been partly dissected and could not be pressure-fixed (Heard et al. 1979).

Electron microscopy was performed on pieces of lung tissue that were diced when fresh, immersed in a 2.5% solution of glutaraldehyde in cacodylate buffer and post-fixed in 1% osmium tetroxide. 1 μm thick sections examined by light microscopy showed some distended alveoli which were selected for electron microscopy. Type I epithelial cells in

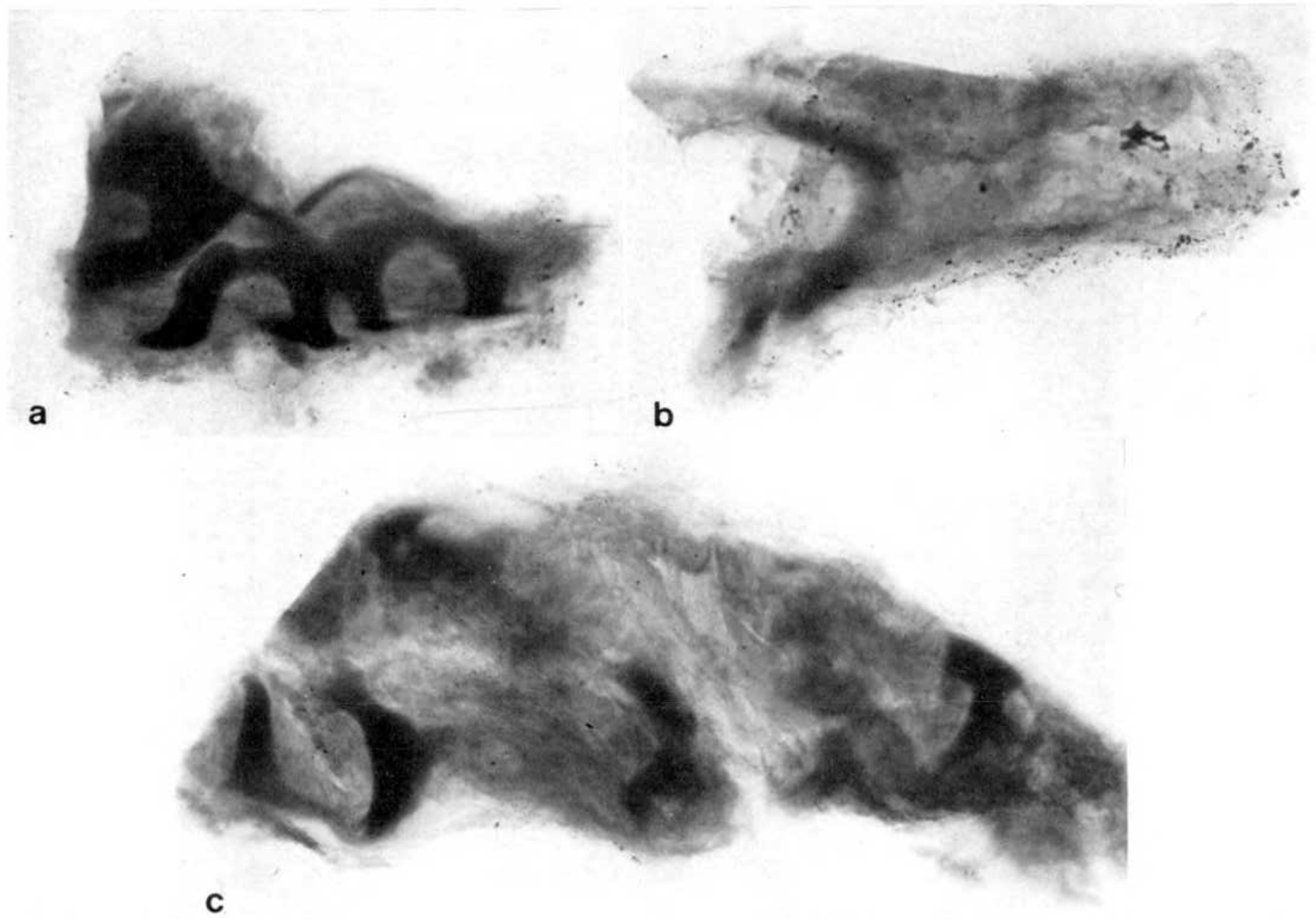

Fig. 3. (*a*) Upper lingular bronchus with normal cartilages present (stained darkly). (*b*) Bronchus to the apical segment, showing partial deficiency of cartilages. (*c*) Bronchus to the posterior segment of the left upper lobe, showing cartilages appearing more widely separated than normal. Specimens stained with acidic toluidine blue and cleared in methyl salicylate. Original magnification × 81

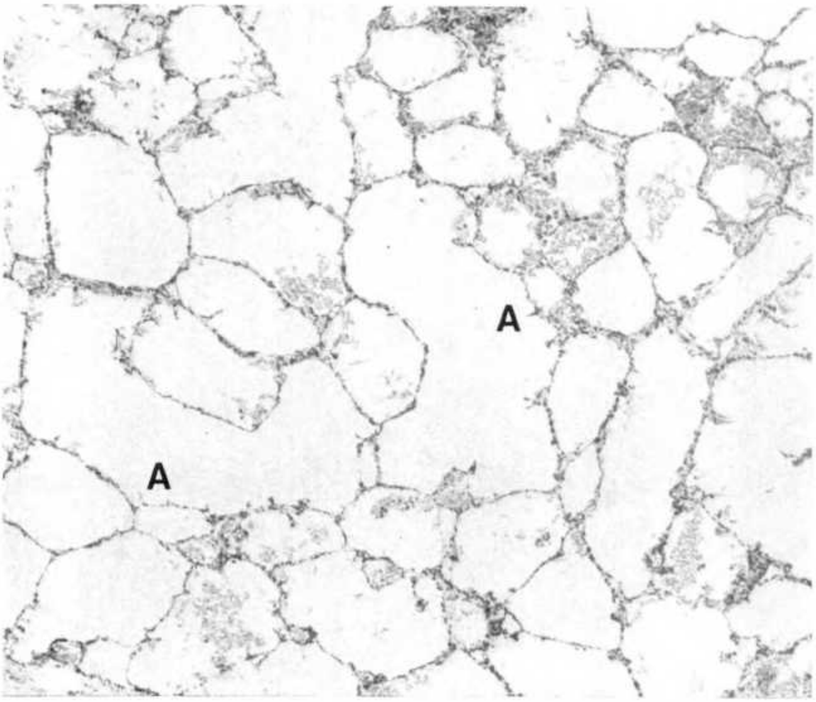

Fig. 4. Posterior segment of left upper lobe showing emphysema with shortening of alveolar walls (A) projecting into the alveolar ducts and reduction in their number. Haematoxylin and eosin, original magnification × 80

some alveoli were swollen, with pale cytoplasm (Fig. 5). Type II epithelial cells were patchy in distribution and did not contain many lamellar bodies. Within alveolar walls, collagen and elastic tissue were present and there were a few eosinophils. Capillary endothelial cells appeared mostly normal but a few were slightly swollen. The cilia of bronchioles appeared normal.

DISCUSSION

Many anomalies of the respiratory tract have been implicated as causes of congenital lobar emphysema, including abnormality or deficiency of bronchial cartilages (Binet et al. 1962; Campbell 1969); extrinsic compression by bronchogenic cysts etc. (Zatzkin et al. 1962); bronchial mucosal folds (Shafir et al. 1976); mucus plugs (Murray et al. 1967); polyalveolar lobe (Hislop & Reid 1970); volvulus of the lobe (Hislop & Reid 1971); associated hypoplastic lung (Henderson et al. 1971); and bronchial atresia or stenosis (Leape & Longino 1964). Only bronchial cartilage defects have been described with any frequency (Stovin 1959) and most of the remaining reported causes have arisen from only one or two case descriptions. The present case is unusual in having two identifiable causes of lobar over-inflation.

Bronchial atresia is rare in association with lobar emphysema. It usually presents late and is often asymptomatic. A total of 37 cases has been reported in the world literature

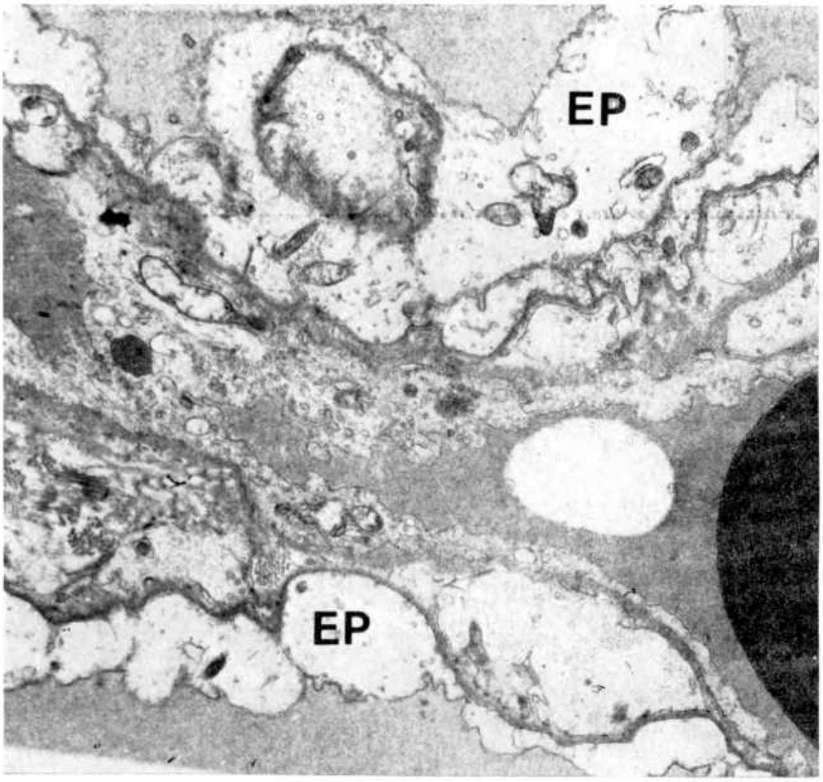

Fig. 5. Ultrastructural demonstration of swelling of some Type 1 epithelial cells on both aspects of an alveolar wall (EP). Electron micrograph, original magnification × 9000

to date (Meng et al. 1978; Massachusetts General Hospital 1979; Robotham et al. 1980).

Most cases have been detected during routine chest radiography in young adults; only rarely has it produced symptoms of chronic cough or recurrent infection and has never previously been associated with respiratory distress in infancy. One case was diagnosed fortuitously at birth when the chest radiograph revealed an opacity at the left apex. This had cleared by six days of age leaving a hyperlucent overinflated lobe which only required removal by 10 years. As in our case the lobe was emphysematous in addition to the bronchial atresia, suggesting more diffuse disease (Robotham et al. 1980). The earliest age of symptomatic presentation prior to our report was five months and this infant also had cystic adenomatoid malformation of the affected lobe (Demos & Teresi 1975). The early presentation of problems in our case probably arose because of the additional bronchial cartilage abnormality.

Characteristically the chest radiograph shows not only an over-inflated lobe but also an extrahilar branching ovoid density representing accumulation of bronchial secretions distal to the atresia. Presumably our case was too young for this to have developed. 24 of the 36 case descriptions have involved the left upper lobe and the majority of these the apicoposterior segment, as in our case.

The over-inflation of the lung is presumed to occur by collateral ventilation through the interalveolar pores of Kohn and inter-respiratory bronchiolar pores which open during inspiration rather than expiration. The persistence of dextrocardia in the absence of cardiac defect is unusual. It is possible that the segment of lung supplied by the atretic bronchus was distended with lung fluid antenatally (Griscom et al. 1969; Robotham et al. 1980), causing compression of other intrathoracic structures from an early stage in gestation. This could result in persistent displacement of structures, even after resection.

Defective bronchial cartilages in the affected lobe have been the generally accepted explanation for congenital lobar emphysema in many cases.

However, it is impossible to say whether this abnormality is the primary cause of the emphysema or is secondarily associated with it. It may be that far more subtle defects of connective tissue in the affected lobe account for the extreme over-inflation which is unparalleled in acquired obstructive defects.

As mentioned in the introduction, the term 'congenital lobar emphysema' is used in this article because it is widely employed clinically for a type of respiratory distress in early infancy. Strictly speaking, however, it would be more precise to use a classification based on morphological characteristics (Heard et al. 1979) until pathogenetic and aetiological factors in emphysema are understood better. The morphological term 'panlobular emphysema' is defined as a form that involves all air spaces beyond the terminal bronchioles in a relatively uniform manner throughout affected lobules. In the present case, the term 'panlobular emphysema of infancy' would therefore be more acceptable to morphologists than 'congenital lobar emphysema'. The terminology will become more uniform as the causes and mechanisms are gradually elucidated. This type of emphysema may be secondary to a congenital defect in the cartilage and not congenital in itself. On the other hand, there may be a more fundamental congenital tissue abnormality at alveolar level to account for the emphysema. Studies of quantitative and qualitative changes in collagen and elastin in the lungs of further similar cases should elucidate this problem. The electron microscope changes were of interest though we feel that they were probably secondary to over-inflation. More studies are again required.

This case illustrates the need for very careful bronchial dissection and histological examination of lung tissue obtained from cases of congenital lobar emphysema.

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TRANSITORY ULTRASTRUCTURAL ABNORMALITIES OF CILIA

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Brompton Hospital, London

Summary

We report a patient with chronic respiratory tract disease and ultrastructural abnormalities of nasal cilia at first interpreted as being consistent with a primary ciliary defect. Subsequent sampling of nasal ciliated epithelium from the same area failed to reveal the defects of structure. Abnormalities of ciliary ultrastructure found on a single occasion, especially in the presence of acute inflammation, should be interpreted with caution.

INTRODUCTION

A number of structural defects of cilia have been described (McDowell et al 1976; Eliasson et al. 1977; Editorial 1979; Sturgess et al. 1979, 1980; Fox et al. 1980) but the significance of such findings is not fully clear. These abnormalities are not necessarily associated with defects of ciliary function. Some previous reports of structural abnormalities have presumed abnormal or absent ciliary motility because of defective mucociliary clearance (MCC). Abnormalities of ciliary structure and function may be either hereditary (primary) or acquired (secondary) and differentiation between these two possibilities on the basis of a single sample may be difficult. Where possible ciliated epithelium should be studied on more than one occasion or from different organs. In post-pubertal males sperm tail ultrastructure may confirm a primary abnormality.

Case Report

The patient, a 12-year-old boy, had wheezed intermittently since the age of 18 months. He had recurrent sinopulmonary infections which improved for several years after adenotonsillectomy at the age of five. Since the age of eight he had continual rhinitis and nasal obstruction. In the two years before presentation there had been recurrent upper and lower respiratory tract infections with cough productive of yellow sputum and a limited response to antibiotics. The patient was atopic and bronchial lability was present on histamine inhalation. Sweat sodium was 26 mmol/litre (normal < 70 mmol/litre). A chest radiograph was normal apart from increased right lower lobe shadowing. There was no evidence of bronchiectasis at bronchography. Sinus radiographs were normal. Sputum culture at various times grew *Haemophilus influenzae*, *Streptococcus pneumoniae*, coliforms and *Pseudomonas aeruginosa*. Nasal culture grew normal flora only. When first studied he had just completed intensive therapy (carbenicillin and gentamicin) for a *Ps. aeruginosa* chest infection and was taking oral aminophylline and nasal beclomethasone dipropionate.

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* Present address: Respiratory Unit, Concord Hospital, Hospital Road, Concord, Sydney, NSW 2139, Australia.

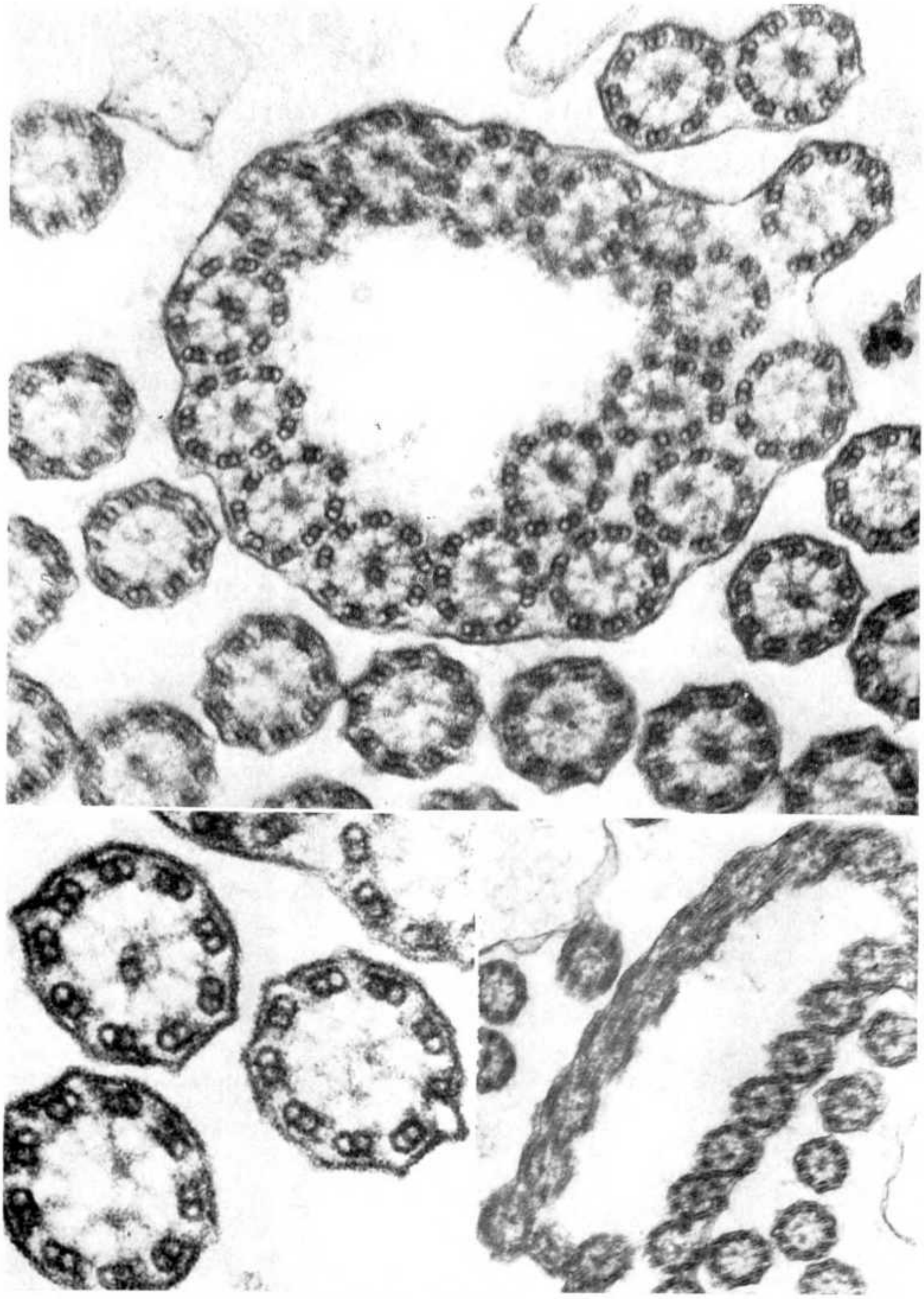

Fig. 1. Above, Transverse sections of cilia, many with absent central tubules and a circlet structure (× 96 000). *Below left,* Absent central tubules (× 160 000). *Below right,* 'Circlet' structure (× 36 000)

Samples of ciliated nasal epithelium were obtained from the inferior nasal turbinate by a brushing technique not requiring local anaesthetic (Rutland & Cole 1980). Ciliary beat frequency (CBF), measured at 37°C by a photometric method (Rutland and Cole 1980), was 13.9 ± 0.4 beats/second (mean ± 1 standard deviation of ten counts). CBF in five age-matched normal subjects was 13.5 ± 1.2 beats/second. We have found that beat frequency in a group of 60 normal adults was 14.0 ± 1.7 beats/second.

Transmission electron microscopy was performed on samples of ciliated epithelium obtained by nasal brushing (Rutland et al. 1982) from the same area as that used for measurement of beat frequency. Four brushings from the inferior turbinate were collected into glutaraldehyde and pooled. Three blocks were studied by light microscopy (1 μm sections) and representative areas chosen for electron microscopy. These were representative of the brushings as a whole. Almost 6000 ciliary profiles were present in the sections examined but only a minority provided transverse sections where optimal ultrastructural detail could be seen. Examination of transverse sections of the 173 such cilia revealed absence of central tubules in 82 (47.4%) throughout the sample (Fig. 1). None of the profiles counted were close enough to the cell's luminal surface to include microvilli; central tubules may be absent in normal cilia at this level. A further nine ciliary profiles consisted of axonemes (ciliary components) arranged peripherally around a clear area in a 'circlet' arrangement, the whole structure being surrounded by one cell membrane (Fig. 1). These forms comprised 0.16% of the 5717 ciliary profiles present in the sections examined. A further 32 (0.56%) ciliary forms were compound cilia of the more usual variety. Dynein arms and radial spokes were normal.

Because of these structural abnormalities and the absence of suitable longitudinal sections of cilia in this sample the patient was studied again six weeks later, at which time he had improved clinically. Therapy at this time consisted of nasal beclomethasone dipropionate alone. The second sample was from the same area as the first. On this occasion CBF was 14.3 ± 0.7 beats/second. On ultrastructural examination of 139 cilia none had absent central tubules and no circlet structures were seen. Pulmonary MCC, measured by an inhaled radioaerosol technique, was normal.

After a further six weeks the same site was brushed again. CBF was 13.0 ± 0.7 beats/second and central tubules were absent in two of 207 (1%) cilia; no circlets were seen.

DISCUSSION

A number of abnormalities of ciliary structure have been described in patients with chronic respiratory disease (McDowell et al. 1976; Eliasson et al. 1977; Editorial 1979; Sturgess et al. 1979; Fox et al. 1980). These include compound cilia, defects of the nine peripheral pairs of tubules, dynein arm defects, radial spoke defects and transposition of ciliary microtubules with absent central tubules low down in the cilium replaced higher up by a peripheral doublet passing centrally (Sturgess et al. 1980). It has been suggested that structural abnormalities of cilia result in impaired MCC (presumably because of defective ciliary function) (Afzelius 1979; Editorial 1979). To date abnormal function of cilia (ciliary dyskinesia) has been reported only with dynein arm defects.

In our patient, a structural defect (absent central tubules) in approximately half the cilia sampled was not associated with a defect in beat frequency. Cilia with absent central tubules may be found close to the cell surface but, because the level at which cilia are cut varies in any one tissue section, it is unusual to find more than an occasional cilium without central tubules. In 20 normal subjects we found absent central tubules in a mean of 0.48% cilia (range 0–3.8%) and in 15 subjects with bronchiectasis central tubules were absent in 0.91% (range 0–4.4%) cilia. The circlet structures, not previously described, may represent a stage in the formation of compound cilia or may be a degenerative change. Another possibility is that they may be protrusions of the cell surface with inclusion of 9 + 0 microtubular structures. It was because of the unusual findings in our first sample and because of the non-invasive nature of the brushing technique that we restudied this patient.

We do not believe that the cilia with absent central tubules and the circlet structures found in this patient have any functional significance. It is unlikely that the finding of such abnormal cilia in the numbers we report represents a sampling error: were this the case we would expect such findings more frequently. Although the possibility of drug-induced ciliary defects cannot be excluded, the only drug administered nasally, beclomethasone dipropionate, was in continuous use throughout. We feel that the absence of both the circlets and the central tubule defect at the second and third examinations implies that these abnormalities were secondary, probably to local inflammation.

Clinical investigation of chronic respiratory tract disease may include examination of ciliary ultrastructure, usually in a nasal or bronchial biopsy. Such samples are commonly obtained during hospital admission for acute illness. To have diagnosed a congenital or primary ciliary abnormality on the first sample alone would have been incorrect. When investigating patients for the possibility of a primary ciliary defect we feel that the results of a sample taken on a single occasion, especially in the presence of infection, should be interpreted with caution. There is a non-invasive technique for obtaining ciliated epithelium which is suitable for repeated studies. It is suggested that, as with the investigation of immunological defects, patients with possible ciliary abnormalities be studied between acute infections and, where possible, on more than one occasion.

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BRONCHOCENTRIC GRANULOMATOSIS AND ADULT RESPIRATORY DISTRESS SYNDROME

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Summary

We describe a case of bronchocentric granulomatosis in a young woman with several unusual features. She developed spontaneous pneumothoraces, diffuse interstitial infiltrates and the adult respiratory distress syndrome during the course of her illness. A pathological diagnosis was not made until treatment with corticosteroids had led to a marked improvement in the patient's condition and an open lung biopsy was performed.

Introduction

Bronchocentric granulomatosis is a recent addition to a long and rapidly growing list of pulmonary hypersensitivity reactions (Liebow 1973). The diagnosis is based upon the recognition of palisading granulomatous reaction under and replacing the bronchial epithelium in small and medium-sized airways. Angiitis may occur but is not a prominent feature. The disease has a favourable outcome. We recently treated a young woman with bronchocentric granulomatosis who developed spontaneous pneumothoraces, acute respiratory failure and the adult respirttory tract symptoms.

Case Report

A 27-year old woman was admitted to hospital with a three-day history of coryza, malaise, headache, non-productive cough and a fever of 38.9°C. Two weeks before admission she was given sulphamethoxazole and doxycycline for a urinary tract infection. Otherwise, her past medical history was unremarkable. There was no history of atopy in the family.

Examination revealed a temperature of 37.8°C and bilateral lower zone râles. A chest radiograph revealed a normal size heart and reticulonodular infiltrates, which were most prominent in the right lower lung field (Fig. 1).

The haemoglobin level was 13.3 g/dl. The white blood cell count was 8600/mm^3 with 90% neutrophils, 9% lymphocytes and 1% monocytes.

She was given penicillin, doxycycline and supplemental oxygen, but three days later developed severe respiratory distress and collapsed. A chest radiograph revealed bilateral pneumothoraces but because of an inability to maintain the P_{aO_2} and of a rising P_{aCO_2}, assisted ventilation was begun. The penicillin and doxycycline were discontinued and ampicillin and gentamicin started. A sputum culture grew *Escherichia coli.*

On the seventh hospital day a transbronchial biopsy specimen was obtained which revealed hyaline membrane formation. Hydrocortisone was begun. On the nineteenth hospital day she was transferred to the University of Southern California-Los Angeles County Medical Center. Blood pressure was then 124/80 mmHg; pulse rate 88/minute; temperature 37.6°C; and respiratory rate 18/minute. There were no rashes or lymphadenopathy. Auscultation of the lungs revealed decreased breath sounds on the left and scattered râles and rhonchi bilaterally. A chest radiograph showed bilateral alveolar and interstitial infiltrates, subcutaneous emphysema and a left pneumothorax.

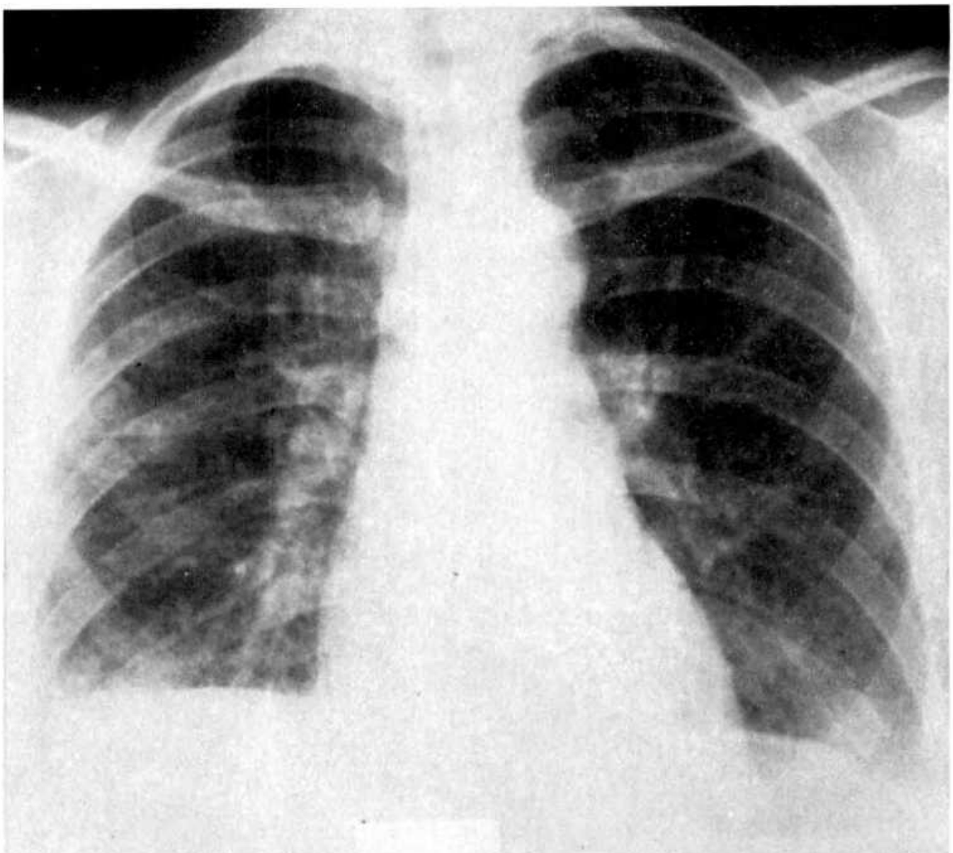

Fig. 1. Chest radiograph on admission shows bilateral reticulonodular infiltrates most prominent in the bases

The white cell count was 18 200/mm^3 with 82% segmented neutrophils, 4% band forms, 8% lymphocytes, 1% monocytes and 2% eosinophils. The platelets were normal and tests for rheumatoid factor, cold agglutinins and antinuclear antibodies were negative. The serological tests for coccidioidomycosis, histoplasmosis, psittacosis, toxoplasmosis and Legionnaire's disease were non-diagnostic. Arterial blood gases on intermittent mandatory ventilation with an $F\text{io}_2 = 0.6$ and 5 cm H_2O of PEEP revealed a pH of 7.49, a $P\text{ao}_2$ of 56 mmHg (7.45 kPa) and a $P\text{aco}_2$ of 34 mmHg (4.65 kPa). She was given tetracycline, erythromycin and hydrocortisone. A repeat transbronchial lung biopsy showed a few alveoli with non-specific inflammatory reaction.

Over the next 12 days her condition improved and she was weaned from mechanical ventilation. The hydrocortisone dosage was reduced and with decreasing doses the eosinophil count in the peripheral blood was noted to rise to 1500/mm^3. An open lung biopsy was performed.

Microscopic examination of the resected lung tissue revealed granulomata in areas of elastic tissue, as demonstrated by special stains, and it was felt that this elastic tissue was representative of bronchioles which had been destroyed by this necrotizing granulomatous process (Figs 2, 3). On culture the lung biopsy tissue did not grow any bacteria, acid-fast bacilli or fungi.

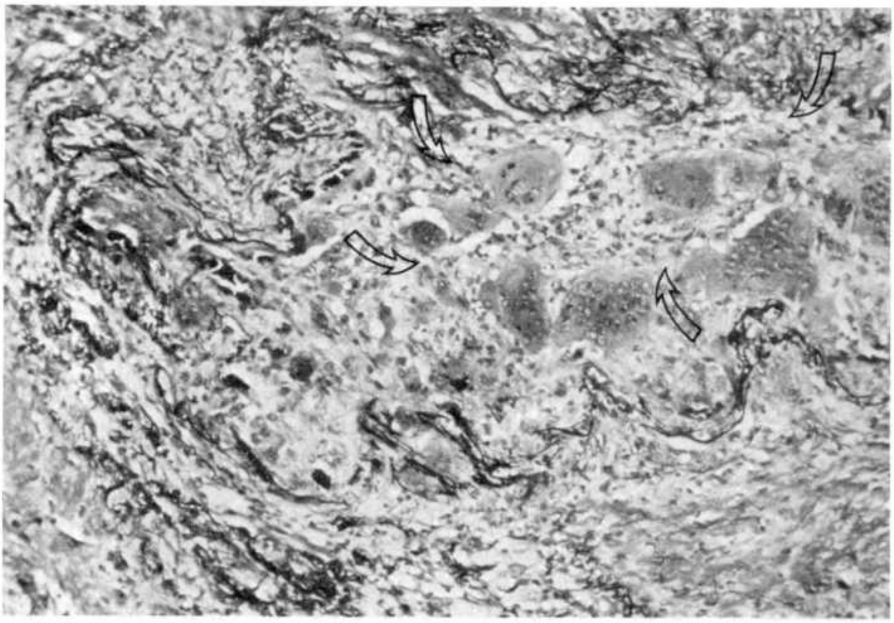

Fig. 2. Lung biopsy. There is exuberant granulomatous replacement of the bronchiolar mucosa with luminal occlusion (arrows). ×400

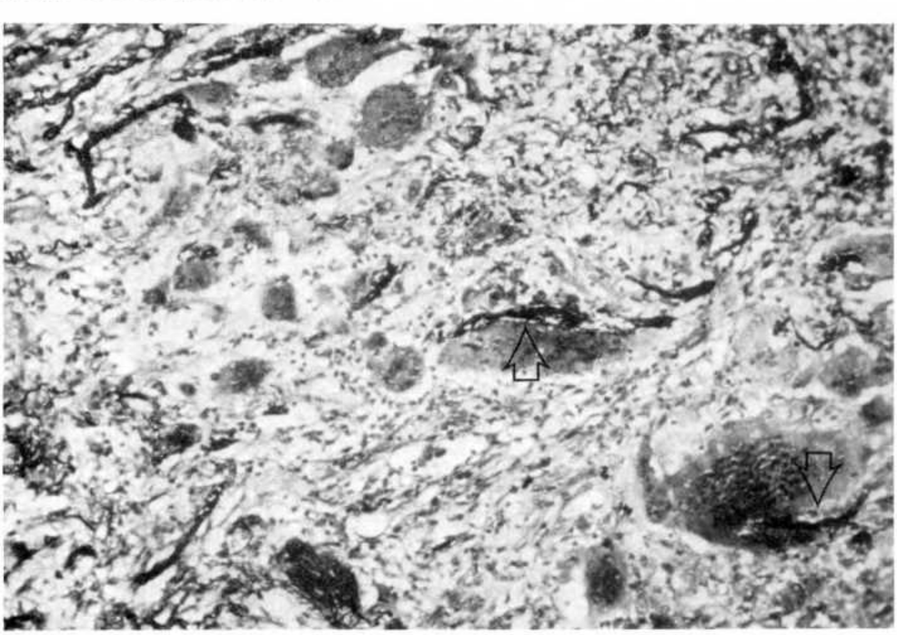

Fig. 3. Lung biopsy. Destruction of the bronchiolar wall is evidenced by giant cell reaction with damaged multi-laminated elastic lamellae (arrows). ×400

DISCUSSION

Katzenstein et al. (1975) described 23 cases of bronchocentric granulomatosis, the histological features of which were similar to that of our patient. Numerous necrotic granulomata, bronchocentric in nature, were seen along with some bronchioles which could only be discerned through the use of elastic stains. We have failed to find reports of another case with a fulminant course characterized by profound hypoxaemia, decreased lung compliance and interstitial hyaline membrane formation. At no time in the early stages was our patient shocked or hypotensive and there was no good evidence of severe pulmonary infection.

Most of Katzenstein's patients exhibited a radiographic pattern of lobar or sublobar consolidation, atelectasis or patchy pneumonic infiltration, but a few had mass-like lesions, nodular and linear densities. Three-quarters had unilateral radiographic findings but, in contrast to our patient, there were no cases of diffuse interstitial or alveolar infiltration.

Our patient differed from those of Katzenstein et al. in several other ways. Pneumothorax was not seen in their patients, nor has it been reported since. Only two of their non-asthmatic patients developed mild eosinophilia but our patient, who had no prior history of atopy or asthma, developed eosinophilia up to 1500/mm^3. The clinical course of our patient was markedly different from the generally benign course noted in others. Finally, multiple transbronchial biopsies failed to reveal the nature of the disease and it was not until an open lung biopsy was performed, much later in the course, that the diagnosis was made. This, once again, demonstrates the need for aggressive biopsy procedures in the face of progressive, diffuse lung disease of unknown aetiology.

The aetiology of bronchocentric granulomatosis remains obscure, but the finding of fungal organisms in the lungs of asthmatics with this disease (Hanson et al. 1977) invites speculation that it may be a type of allergic reaction to these fungi. This association is not clearly seen in the non-asthmatic patient, however, and in our patient no fungal elements were seen in the resected lung tissue.

Our patient had received sulphonamides before admission and sulphonamides have been reported to cause a vasculitis of the granulomatous type (Rosenow 1972) but these granulomata are angiocentric rather than bronchocentric. Sulphonamides have also been reported to produce pulmonary infiltration with eosinophilia but bronchocentric granulomata are not seen in this disorder either and it seems unlikely that the sulphonamide was an aetiological agent in our patient's illness.

In summary, we have described a patient with bronchocentric granulomatosis in whom the disease pursued an unusual and fulminant course. We suggest that bronchocentric granulomatosis be added to the burgeoning list of disorders which may on occasion be associated with the adult respiratory distress syndrome.

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ACUTE PULMONARY OEDEMA FOLLOWING GRAND MAL EPILEPSY AND AS A COMPLICATION OF ELECTRIC SHOCK THERAPY

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Summary

Two patients are described who developed acute pulmonary oedema: the first following a grand mal epileptic seizure of idiopathic origin, the second following electric shock therapy (ECT) for depression. Neither patient had any detectable underlying cardiopulmonary disease. The first patient recovered spontaneously but the second patient died of fulminant pulmonary oedema. This is the first report of neurogenic pulmonary oedema following ECT

INTRODUCTION

Pulmonary oedema has long been recognized as an occasional complication of epileptic seizures and sporadic cases have been reported since the turn of the century. I report two more, the second of which has an additional unusual feature in that the patient's seizure was induced by electroshock for the treatment of depression.

Case Reports

Case 1

A 35-year-old man with a history of mental retardation and idiopathic epilepsy from birth presented with a sudden onset of breathlessness and cough following several grand mal epileptic seizures. There was no previous history of any pulmonary or cardiovascular disease. On examination, apart from a low grade temperature of 37.4°C, there were no abnormal physical signs (including the heart and lungs). A chest radiograph (Fig. 1) showed fluffy shadows in the left lung, though sparing the left base, and in the upper third of the right lung. Repeated auscultation by several physicians confirmed the absence of abnormal auscultatory findings. An electrocardiogram showed a short P–R interval of 0.11 seconds but was otherwise completely normal. Sputum examination showed only mixed flora and was of poor quality. White blood cell count was 12 900/mm^3. Transtracheal aspiration was performed since it was thought highly probable that the patient had aspirated during his seizure. Subsequent culture of the transtracheal aspirate was sterile. A further chest film was taken almost exactly 24 hours later and was completely normal. Any confusion with another patient's radiographs was excluded by certain peculiarities of the patient's bony skeleton. The white blood cell count had fallen to 7000/mm^3. The patient was discharged after a hospital stay of 72 hours.

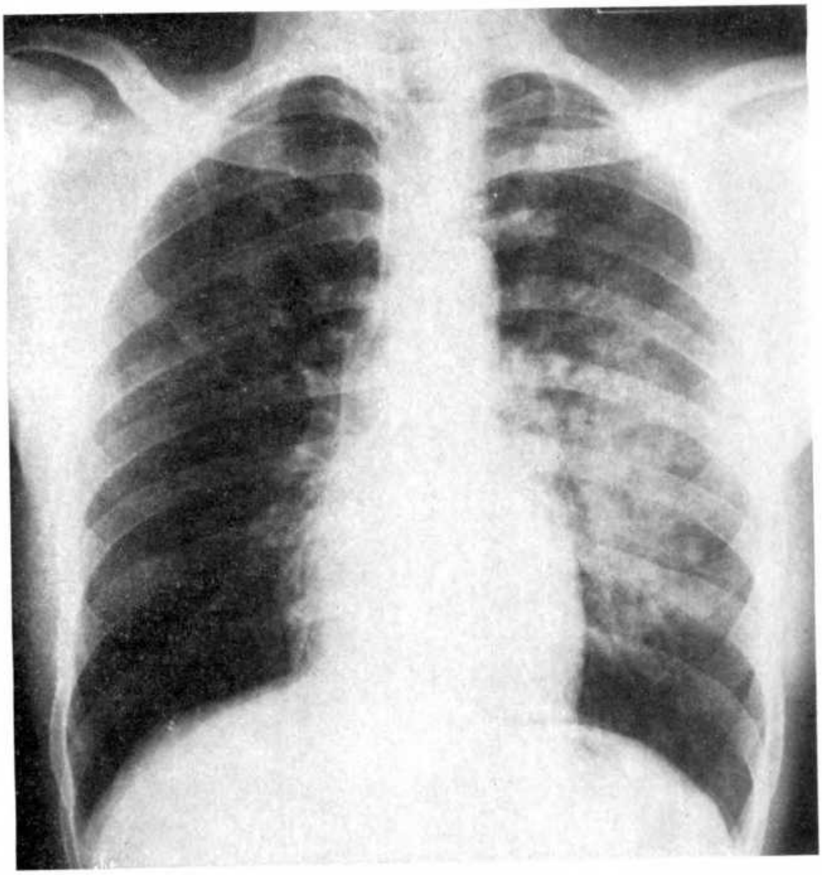

Fig. 1 Chest radiograph of Case 1, a 35-year-old man, following several grand mal seizures. The radiograph was completely normal within 24 hours

Case 2

A 44-year-old housewife had suffered from severe depression for approximately seven years and did not respond to treatment with tricyclic antidepressants. A feature of her depressive illness was a refusal to eat because of soreness of her tongue and oral cavity, though no lesions were visible within the mouth. As a consequence of her self-imposed starvation, she became extremely underweight (mean weight 35 kg), anaemic (Hb 7.2 g/dl) and hypoproteinaemic (albumin 2.04 g/dl). She had no history of prior cardiopulmonary disease and, apart from the emaciation, had no abnormal physical findings. A chest radiograph and electrocardiogram were normal. She underwent a single treatment with unilateral non-dominant ECT under sodium pentothal anaesthesia and succinylcholine as a muscle relaxant. The procedure was noted by the operator to be 'poorly tolerated'. She recovered from the anaesthesia normally, but was noted to be breathless one hour later. She expectorated frothy, blood-stained sputum and was cyanosed. Auscultation revealed widespread bilateral crackles throughout the chest, including the apices. Her blood pressure was 100/80 and a chest radiograph (Fig. 2) showed widespread shadowing suggestive of pulmonary oedema. The heart size and the ECG were normal. Arterial blood gas analysis showed severe hypoxia, hypercapnia and respiratory acidosis. Despite vigorous efforts to treat the pulmonary oedema, she continued to deteriorate and suffered a cardiopulmonary arrest 16 hours after the ECT had been administered. Attempts at resuscitation were unsuccessful. Permission for autopsy was not obtained.

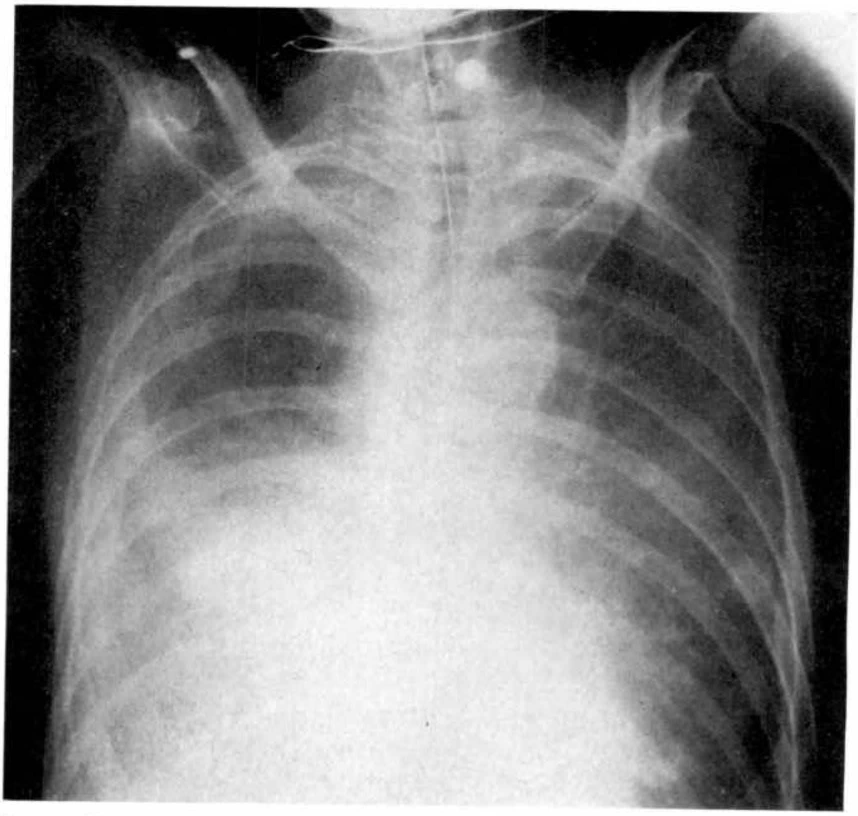

Fig. 2. Chest radiograph of Case 2, a 44-year-old housewife who became severely dyspnoeic one hour after electroshock therapy. The patient died 16 hours after the procedure. (Portable, decubitus antero-posterior film)

Discussion

Isolated case reports of pulmonary oedema as a transient phenomenon occurring after one or more grand mal seizures have appeared since the first report in 1908 (Shanahan 1908). In all the reported cases, the oedema occurred within three hours of the end of the seizures and produced symptoms of respiratory distress of varying severity, but most often breathlessness, cough, haemoptysis and, occasionally, transient fever. The typical auscultatory findings of pulmonary oedema are usually present, but occasionally may be absent in spite of confirmatory radiological appearances (Huff & Fred 1966). The physical signs and radiological abnormalities may be those of 'classic' pulmonary oedema or they may be unilateral or show a predilection for the upper rather than the lower zones of the lung field (Amigable & Farhondi 1971; Malik et al. 1973; Greene et al. 1975). Amigable and Farhondi (1971) commented in their case report and literature review that postictal patients should have their chests examined closely, clinically and radiologically, since postictal pulmonary oedema may be commoner than was hitherto suspected. Despite this, the complication may still frequently go unsuspected; in one case report (Adornato 1976) of 'factitial' pulmonary oedema following a major seizure, the condition was ascribed to aspiration of gastric contents and the pink-coloured sputum to the suspicion that the patient might have consumed a strawberry milkshake prior to the seizure.

Ohlmacher (1910) reviewed 203 deaths at the Ohio Hospital for Epileptics: 41 deaths followed an attack of epilepsy or the patient was found unexpectedly dead in bed. Of these 41, pulmonary oedema was the only abnormality found at autopsy in 13.

Postictal pulmonary oedema may be differentiated readily from aspiration pneumonia by the rapidity with which it disappears without specific treatment (Chang & Smith 1967; Bloom 1968; Amigable & Farhondi 1971; Malik et al. 1973; Archibald & Armstrong 1978) as occurred in the first patient described in this report; the ranges of time for complete resolution varies in the reports from six hours to four days, a shorter time than that of resolution of aspiration pneumonia.

The cause of the grand mal seizures appears to be irrelevant and reports of postictal pulmonary oedema have included patients whose epilepsy was post-traumatic (Huff & Fred 1966), idiopathic (Shanahan 1908; Huff & Fred 1966; Chang & Smith 1967; Bloom 1968; Amigable & Farhondi 1971; Malik et al. 1973; Greene et al. 1975; Archibald & Armstrong 1978) or was secondary to subarachnoid haemorrhage (Chang & Smith 1967) or intracranial tumour (Chang & Smith 1967; Greene et al. 1975). In addition, it has been reported as a complication of intracerebral haemorrhage (Weisman 1939), insulin shock therapy and following ECT (Malik 1972). In the latter report, however, it occurred following the development of a severe cardiac arrhythmia and was felt to be cardiogenic in origin. In the second patient reported here, no disturbances of heart rhythm occurred at any time during or after her ECT.

Acute pulmonary oedema may be induced in experimental animals by raising intracranial pressure (Campbell et al. 1949; Harrison & Liebow 1952; Bowers et al. 1971; Breshear & Pamintuan 1971) or by direct trauma to the brain (McKay 1950) and prevented by prior pulmonary denervation (McKay 1950; Moss & Stein 1976) or administration of naloxone (Peterson et al. 1980). Grand mal epileptic seizures are known to be associated with rises, often considerable, in intracranial pressure. In one series of human experiments White et al. (1961) induced seizures with intravenous pentylenetetrazol in unselected epileptics. Concomitant with the seizure were rises in systemic blood pressure (mean rise 85 mmHg systolic, 42 mmHg diastolic) and cerebrospinal fluid (CSF) pressure measured at the lumbar spine (mean rise 549 mmH_2O, range 270–800). Breshear and Pamintuan (1971) showed that increasing the CSF pressure causes strong α-adrenergic stimulation which elevates pulmonary arterial and venous pressures and β-adrenergic stimulation which elevates pulmonary blood flow; they concluded that pulmonary oedema could result from this intense distension of the pulmonary capillary bed. The underlying mechanics have been well reviewed (Theodore & Robin 1976).

The advice of Amigable and Farhondi (1971) is worth reiterating. Pulmonary oedema may be a a commoner sequel to grand mal epilepsy than the few case reports of the condition suggest and it may become obvious only when it is severe enough to produce symptoms. Thorough chest examination is advisable in postictal patients. The development of breathlessness, cough, haemoptysis or other signs of respiratory impairment in patients who have undergone ECT should raise the suspicion that they may have developed this form of neurogenic pulmonary oedema, here described for the first time as a complication of ECT.

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RESTRICTIVE PATTERN OF LUNG FUNCTION FOLLOWING PSITTACOSIS TREATED WITH CORTICOSTEROIDS

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Psittacosis is a well recognized cause of pneumonia, although in most cases infection remains mild or subclinical. Some patients are more severely ill with involvement of the respiratory, cardiovascular and central nervous systems. The chest radiograph often shows areas of consolidation greater than the physical signs would suggest. Recovery may be prolonged.

A case of severe pneumonia due to psittacosis is reported in which a severe restrictive pattern of lung function complicated recovery. This has been described following mycoplasma pneumonia with evolution into diffuse interstitial fibrosis (Kaufman et al. 1980) but not as far as we can discover following psittacosis. Treatment with corticosteroids was associated with complete resolution of the lung function and chest radiograph abnormalities after nine months.

Case Report

A 53-year-old woman presented with a two-week history of dyspnoea and night sweats. On examination, she was very ill and cyanosed with a respiratory rate of 60/minute. Her temperature was 38°C, pulse rate 120/minute and blood pressure 150/90. There were reduced breath sounds at both lung bases and coarse crackles were heard throughout both lung fields. Investigations revealed: Haemoglobin 12.7 g/dl; white cell count 22 100/mm^3 with 98% neutrophils. Breathing air arterial oxygen tension ($P\text{a}O_2$) was 4.9 kPa and carbon dioxide tension ($P\text{a}CO_2$) 4.7 kPa. Her chest radiograph showed widespread bilateral consolidation (Fig. 1). After sputum had been obtained for culture and blood for culture and serology, treatment was started with oxygen and intravenous ampicillin, cloxacillin and gentamicin.

Forty-eight hours later her $P\text{a}O_2$ was 3.9 kPa and $P\text{a}CO_2$ 6.0 kPa on 60% oxygen and she was transferred to the intensive care unit. Mechanical ventilation was started with a tidal volume of 770 ml and a minute volume of 10.8 litres and despite an inflation pressure of 35 cmH$_2$O an $F\text{I}O_2$ of 80% and 5 mmHg PEEP, $P\text{a}O_2$ remained low at 5.6 kPa. By day 8, with a tidal volume of 800 ml and a minute volume of 16.0 litres, her arterial blood gases had improved so that an $F\text{I}O_2$ of 38% was required to maintain her $P\text{a}O_2$ at 8.5 kPa and her $P\text{a}CO_2$ at 5.6 kPa. By day 8 her haemoglobin had fallen to 9.2 g/dl and on day 10 she was transfused 3 units of packed red cells and a tracheostomy was performed. Within 24 hours of transfusion, her respiratory condition became much worse, clinically, physiologically and radiologically. She was ventilated with a tidal volume of 800 ml and minute volume of up to 20 litres and required an inflation pressure of 48 cmH$_2$O and an $F\text{I}O_2$ of 50% to maintain her $P\text{a}O_2$ of 7.4 kPa. Thereafter she recovered, sufficiently to stop mechanical ventilation after 26 days and her tracheostomy was allowed to close, but she remained breathless (respiratory rate 50/minute) with a tachycardia (pulse rate 120/minute) and on air her $P\text{a}O_2$ was 7.1 kPa. Oxytetracycline 500 mg six-hourly was started. A week later when she was still breathless, spirometry showed FEV$_1$ 1.1 litres, FVC 1.1 litres (predicted 2.6 litres) and peak flow rate 325 litres/minute. The chest radiograph showed patchy residual shadowing throughout both lung fields and prednisone was started at a dose of 30 mg daily.

Four weeks after admission the diagnosis of psittacosis was made on an eight-fold rise in complement-fixation test titre and further questioning revealed that she had eviscerated four rough-plucked ducks 10 days before admission, from which it is thought she contracted the disease.

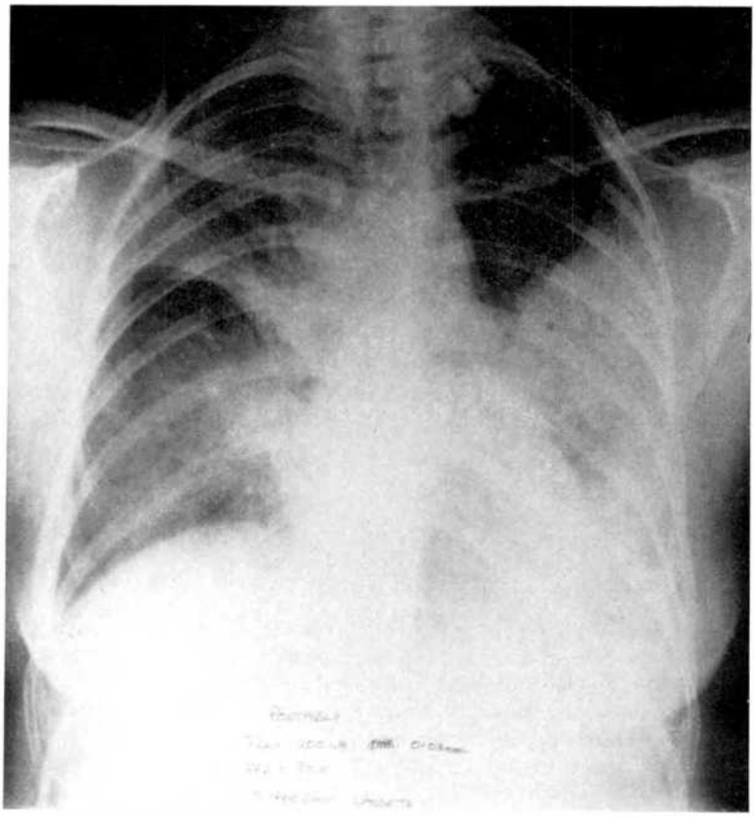

Fig. 1. Chest radiograph on admission showing widespread areas of consolidation due to psittacosis pneumonia

A month later, nine weeks after the onset of her illness, her FVC was still only 1.15 litres. Over the next three and a half months her condition slowly improved, FVC increased to 2.0 litres and prednisone was tailed off. Oxytetracycline was continued while she was receiving steroids in an attempt to prevent recrudescence.

Six months after admission, lung function tests showed FEV_1 1.9 litres FVC 2.0 litres (predicted 2.6 litres), TLC 3.2 litres (predicted 3.9 litres) indicating residual restriction and carbon monoxide transfer factor was 4.5 mmol/minute/kPa (predicted 7.0 mmol/minute/kPa). The inspiratory volume flow curve showed reduced flow, reflecting either some extrathoracic upper airway narrowing or residual restriction. There was no evidence of intrapulmonary airway narrowing.

After nine months lung volumes and carbon monoxide transfer factor were normal (FEV_1 2.3 litres, FVC 2.7 litres, TLC 3.9 litres, carbon monoxide transfer factor 5.6 mmol/minute/kPa). Her volume–flow loop and chest radiograph were also normal.

DISCUSSION

This case illustrates a severe case of psittacosis complicated by severe pneumonia, with features of the adult respiratory distress syndrome and during convalescence a severe restrictive pattern of lung function. Apart from psittacosis, additional factors leading to adult respiratory distress syndrome in this patient were thought to be prolonged oxygen therapy ($F_IO_2 > 40\%$ for five days and $> 80\%$ for two days), intermittent positive pressure ventilation and blood transfusion.

Pulmonary fibrosis following severe acute respiratory failure from diverse causes is recognized (Zapol et al. 1979). Pulmonary function after prolonged mechanical ventilation with high concentrations of oxygen has also been studied but complications due to oxygen toxicity are thought to be rare (Gillbe et al. 1980). A restrictive pattern of lung function is commonly seen during the acute stage of atypical pneumonia (52%) but it is very rare during convalescence although an obstructive pattern may persist for some weeks (Benusiglio et al. 1980). Diffuse interstitial fibrosis has been described following mycoplasma pneumonia and it it possible that high doses of corticosteroids may prevent the evolution of pulmonary fibrosis by influencing fibroblast proliferation.

Our patient had a severe restrictive pattern of lung function following her psittacosis pneumonia with persistent tachycardia, tachypnoea and hypoxaemia. It was felt possible that she had a post-infective alveolitis which was likely to progress to pulmonary fibrosis and she was therefore started on prednisone 30 mg daily. This was tailed off over four and a half months and by nine months her lung function and chest radiograph had returned to normal. We think it likely that steroid therapy favourably influenced her clinical course but cannot exclude the alternative explanation that her complete recovery was due to slow spontaneous improvement.

This patient is part of a recent outbreak of psittacosis in Norfolk (Andrews et al. 1981).

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Br. J. Dis. Chest (1982) *76*, 202

Short Communication

A COMPARISON OF SUSTAINED-RELEASE TERBUTALINE AND ORDINARY TERBUTALINE IN BRONCHIAL ASTHMA

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Summary

The effects and side effects in steady state of a sustained-release preparation of terbutaline 7.5 mg twice daily were compared with ordinary tablets 5 mg three times daily. The study performed for two weeks was double-blind, double-dummy, cross-over with randomized allocation of the drugs. 20 patients completed the trial and the results show higher mean morning PEFR values and a tendency to milder side effects with depot tablets.

Introduction

Terbutaline sulphate has a well-documented bronchodilating effect with a duration of six to eight hours (Formgren 1970). In an attempt to extend the duration and to change the dosage regimen from three times a day (Formgren 1975) to twice a day, a sustained-release preparation of terbutaline sulphate was formulated. It was hoped also that side effects might be reduced if a smoother plasma concentration time profile could be achieved.

The present study compared the effects on peak flow and symptoms and side effects of depot tablets 7.5 mg twice daily with those of ordinary tablets 5 mg three times a day.

Patients and Methods

Twenty-three patients, seven men and 16 women, mean age 43 years (range 19–65), with chronic bronchial asthma and reversibility of airflow obstruction of $\geq 20\%$ entered the study. Before the study, all patients used β_2-stimulating drugs as aerosol, 16 were on oral therapy with terbutaline, seven on theophylline preparations, three on oral corticosteroids, 13 on beclomethasone aerosol, two on disodium cromoglycate, and two on ipratropium bromide. During the study, the only bronchodilator allowed, besides the test drugs, was a short-acting aerosol, rimiterol. Patients who used disodium cromoglycate or steroids before the study continued this treatment with constant dosages.

The patients were divided into two groups, depending on the severity of their asthma. One ($n=8$), called 'severe asthma', was considered to require additional bronchodilators during the study and was therefore prescribed a regular intake of rimiterol with the administration of the test drugs. The other ($n=15$), called 'moderate asthma', was judged not to require extra bronchodilators besides the test drugs.

The study was double-blind, cross-over with randomized allocation of the drugs. It was performed during two consecutive weeks. For one week, patients received ordinary tablets (5 mg) three times a day with six hours between the dosages during the day and 12 hours at night and dummy depot tablets twice daily and for the second week, depot tablets (7.5 mg) twice daily with an interval of 12 hours and dummy ordinary tablets three times daily.

The patients were asked to measure and note their peak expiratory flow rate (PEFR) with a mini-Wright peak flow meter each morning and evening before drug intake. They were also asked to note in their diary card dyspnoea and cough according to a scoring system graded 1 to 4 (1 was 'none' and 4 was 'severe') and side effects if they had any. Use of extra aerosol rimiterol was allowed when needed, but not in the three hours before PEFR measurements. The number of inhalations and the time were noted. The preference of period was noted at the end of the study both concerning asthma symptoms and side effects.

The statistical evaluation was performed according to two-sided t-test and Wilcoxon's signed rank sum test (symptom scoring). The mean values of all parameters during the last five days (steady state) in each period were calculated. Statistical analysis was performed on the whole patient group who satisfactorily completed the trial ($n = 20$) and also on the 'moderate asthma' group ($n = 14$). The number of patients in the 'severe asthma' group, after exclusions, was too small ($n = 6$) for statistical evaluation.

Table I. Symptom score (1–4), aerosol consumption and PEFR values for all patients and the 'moderate asthma' group (Mean values and S.E.M.)

Variables	*All patients* ($n = 20$)		*'Moderate asthma' group* ($n = 14$)	
	Ordinary tablets (5 mg × 3)	Depot tablets (7.5 mg × 2)	Ordinary tablets (5 mg × 3)	Depot tablets (7.5 mg × 2)
Dyspnoea (night)	1.27 ± 0.09	1.25 ± 0.08	1.21 ± 0.09	1.14 ± 0.07
Cough (night)	1.28 ± 0.10	1.12 ± 0.06	1.26 ± 0.11	1.13 ± 0.08
Use of aerosol (night)	0.95 ± 0.43	0.90 ± 0.37	0.69 ± 0.37	0.61 ± 0.32
PEFR (morning)	361.69 ± 20.88	378.53 ± 18.80	363.75 ± 25.28*	391.38 ± 21.22*
Dyspnoea (day)	1.45 ± 0.15	1.51 ± 0.11	1.40 ± 0.18	1.41 ± 0.13
Cough (day)	1.31 ± 0.14	1.18 ± 0.07	1.20 ± 0.13	1.17 ± 0.10
Use of aerosol (day)	1.77 ± 0.63	1.43 ± 0.42	1.64 ± 0.66	1.57 ± 0.59
PEFR (evening)	412.33 ± 18.25	408.42 ± 16.61	422.40 ± 23.26	420.25 ± 19.86

* Significance of difference, $P < 0.05$. All other differences were not significant.

RESULTS

Of the 23 patients entering the trial, three were excluded from all statistical evaluations; two had taken their 'own' bronchodilators during the study and one did not complete the trial because of tremor and palpitations during the period with ordinary tablets.

Table I shows the results. The mean morning PEFR value in the depot tablet period was higher than that in the ordinary tablet period. The difference was statistically significant ($P < 0.05$) when calculations were performed on the 'moderate asthma' group, but not when the 'severe asthma' group was included. The decrease in PEFR between evening and morning ('dipping') was greater during the tablet period in the 'moderate asthma group', (14%) compared to the the depot tablet period (7%) ($P < 0.10$). There were no significant differences between the two treatments in the other recorded measurements.

Eight patients reported side effects during the study. Two patients noted tremor with both ordinary and depot tablets and one patient with ordinary tablets only. The other side effects reported were headache, nausea, tiredness etc. (two patients with both preparations, two with depot tablets and one with ordinary tablets).

More patients preferred the depot tablets than the ordinary ones, both for better effect (six patients preferred depot tablets, three ordinary tablets, 11 had no preference) and milder side effects (five patients preferred depot tablets, one ordinary tablets, 14 had no preference). These differences were not statistically significant.

DISCUSSION

A sustained-release preparation has several potential advantages in the treatment of chronic asthma. A twice-daily dosage (morning and evening) gives a regular dosage over the day, which is an advantage from the pharmacokinetic point of view. Patient compliance should also increase (Gatley 1968). The symptoms of nocturnal asthma and 'morning dippers' can be improved by slow-release bronchodilators (Turner-Warwick 1977).

Terbutaline depot tablets have an adequate bio-availability profile for a twice daily dose regimen and, at steady state, give a smoother plasma concentration curve than ordinary tablets three times daily (Nyberg & Kennedy 1980).

The result of the present study, where all recordings were performed by the patients themselves, indicates that terbutaline in sustained-release form administered twice daily gives the same (for one patient group better) therapeutic effect and a tendency to milder side effects than ordinary tablets given three times daily. These results agree with those of a similar study (Tandorf et al. 1981).

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ERRATUM

Reference No. 8 on page 87 of the *British Journal of Diseases of the Chest* Vol. 76 (1982) should read: 'Leslie, R. D. G., Barnett, A. H. and Pyke, D. A. (1979). Chlorpropamide alcohol flushing and diabetic retinopathy. *Lancet 1,* 997.'

B. J. Dis. Chest (1982) *76*, 205

BOOK REVIEWS

Respiratory Medicine (*Concise Medical Textbook*)

David C. Flenley

London: Baillière Tindall. 1981. Pp. viii+263. Price £6.50

Professor Flenley has set out to write a textbook for senior medical students and candidates for higher qualifications in medicine and expresses the hope that the book will interest general physicians as well. In my view he has succeeded in these aims. He has written an accurate, concise and readable textbook which can be highly recommended. His background is physiological and therefore the scientific basis of the subject is covered, but he does not hesitate to identify areas of ignorance, nor does he embark on reviews of confused literature!

Inevitably there are a few lapses. Lactic acidosis, which he admits is rare in respiratory failure, is awarded nearly a page (including a diagram). On the other hand his advice about the management and therapy of asthma was lower than his general standard. I suspect it would be difficult to obtain a clear idea of how to manage asthma in practice from this description. I do not agree that strongly positive skin tests indicate beclomethasone (presumably inhaled). Not everyone would agree that injections of tetracosactrin were ideal for children and the indications for oral corticosteroids are not clearly expressed. I felt the impression might come across that up to 10 mg prednisolone daily is safe in adults. Whilst side effects are relatively slow to develop at this dose, it would be unwise to give the impression that this level of corticosteroid therapy should lightly be continued in the long term.

However, it is much easier to criticise a good book than to write one. Most of my criticisms are trivial. A normal right lateral chest X-ray is incorrectly projected for a British audience (although there is a correct one on page 225). I did not think it was worth repeating the X-ray of middle lobe collapse in the section on tuberculosis, particularly as this is not a particularly characteristic appearance of tuberculosis in practice. Otherwise the X-ray sketches were generally clear and helpful.

Achalasia and other oseophageal or gastric abnormalities can cause spill-over and thereby recurrent or chronic pulmonary infections or abscess. This is much commoner than, for example, amoebiasis and the importance of a barium swallow could be emphasized. I suspect the inclusion of ampicillin with benzyl penicillin and metronidazole in the treatment of lung abscess is a publishing error. If not it probably ought to be! I am not sure that atelectasis is the commonest sign of lung cancer, nor am I sure that the statement 'Today lung cancer is the major single problem in respiratory medicine' is true or useful!

The style is clear and concise, and single author textbooks are refreshing. There is, however, an irritating tendency for verbs to be apparently randomly in the present or future tense, even within the same sentences.

Professor Flenley divides tuberculosis into primary and post-primary tuberculosis. I cannot criticise him for this as it is a universal tradition in all respiratory medical textbooks. However I myself have never found it a particularly useful division, either conceptually or in practice. It is generally suggested that military tuberculosis, tuberculous meningitis and tuberculous pleural effusions occur in primary tuberculosis and that post-primary tuberculosis is predominantly represented by breakdown of pulmonary primary disease to cause respiratory tuberculosis. However, clinically any type of tuberculosis can occur in any patient, although there may be age and racial tendencies. It seems to me that tuberculosis is, as usual, an interaction of the seed and the soil. The individual may be susceptible, having never met tuberculosis previously, and may have either a constitutionally weak or strong tendency to resist the infection. If clinical disease ensues, this can as well be mild open respiratory tuberculosis as more virulent disseminated tuberculosis. If the episode is fought off, then a degree of immunity is built up which helps resist further attacks. However, exposure of individuals who are relatively immune (either as a result of previous infection or of BCG inoculation) to subsequent high levels of tuberculous infection can sometimes cause a clinical infection. Furthermore the level of immunity can be suppressed, for example by intercurrent illness, immunosuppression and drugs. My suggestion is that we should view all tuberculous infections as potentially similar, with varying degrees of immunity in the host, either congenital, or acquired as a result of previous exposure, or of BCG.

Nevertheless, this should not take away from Professor Flenley's excellent concise textbook. I would strongly recommend it for any pre- or postgraduate student and several copies should be on the shelves of every medical school library.

MALCOLM GREEN

Progress in Respiration Research, 16. Gas Exchange and Function of Normal and Diseased Lungs

J. Piiper and P. Scheid

Basel: Karger. 1981. Pp. xvi+320. Price SFr. 198

This book publishes the contributions made to a satellite symposium of the 28th International Congress of Physiological Sciences, held in the Max Planck Institute in Gottingen. In its 317 pages there are some 70 papers, so that necessarily the papers are short, and in general the reference lists are dominated by the authors or the author's school.

One of the problems in publishing the proceedings of a conference is that contributions are not submitted to the scrutiny of referees. This difficulty is usually circumvented in the discussion which follows each paper, so that views other than those adumbrated by the authors receive an airing. The discussion at this conference was not published, so that each paper sets out briefly the present status of the author's views, unmodified by outside influences. Thus the book records faithfully the work being pursued in a whole variety of areas and countries, but nowhere are the conflicting views reconciled. This may indeed be an advantage, since almost every paper can be seen to be contradicted by some other, and hence to be controversial. The controversies aired include the various influences affecting mixing in the gas phase, the transfer of carbon monoxide across phase boundaries and whether augmented transfer exists, and a variety of mathematical model analysis with different conclusions. The role of the musculoskeletal system in ventilation receives attention as does reaction kinetics of carbon dioxide and other biochemical and enzymatic functions.

The book contains a multicoloured vignette of the current status of research into the gas exchange function of the lung. The vignette is a miniature and produced in the inimitable editorial style of Karger. Volume number 16 is a well-matched stable companion to its predecessors.

G. CUMMING

Manual of Pulmonary Procedures

Stephen J. Jay and Robert B. Stonehill

Philadelphia: W. B. Saunders. 1980. Pp. xii+187. Price £7.00

There is much good common sense in this book, but perhaps because it is presented as a pocket manual, its descriptive material tends to be somewhat dry and lacking in interest.

The editors open with a diffident and disarming preface, which tells us that the first half of the handbook provides descriptions of common procedures summarized in a practical fashion, while the second part concentrates on a background of a 'core of clinically pertinent data' with historical sketches and references to the literature. As it turns out, these two distinct aims become somehow confused, and in many respects both parts of the book would benefit from tighter editing.

This manual already has an old-fashioned air about it. This may have to do with typographical setting as much as with anything else, but as is so often the case with medical texts, publication is overtaken by events. There is, for example, no description of either bronchoscopic or bronchographic techniques, although transtracheal aspiration by puncture of the cricothyroid membrane is still accorded a detailed description. This latter technique is rarely indicated now that fibreoptic bronchoscopy is within the competence of most chest physicians. I am afraid that this book, written and published in the USA, falls short of the requirements which most chest units in this country would set, and I do not think it will win a place on many bookshelves here.

W. P. U. KENNEDY

Principles of Clinical Measurement

M. K. Sykes, M. D. Vickers and C. J. Hull

Oxford: Blackwell Scientific. 1981. Second Edition. Pp. x+325. Price £21.00

Any doctor must be 'jack of many trades', and the general practitioner more than most, but possibly he should also be master of at least some. The number of trades invoked in the practice of anaesthesia, if this book be a guide, is indeed daunting. To the practising physician, for whom this book is also intended, the scope is exhausting, reviving half-forgotten memories of school physics of long ago, but here brought up to date. Clearly a physicist would be required to vouch for the accuracy of much of the information in this book, and a mere physician can only admit to applying the test of understanding (or failing to do so) of the authors' descriptions. On this score, therefore, the authors largely succeed, at least with this test market. However, I still do not understand how a quadrupole mass spectrometer works (and my charitable fear that this ignorance *may* be shared by the authors is clearly an unfounded slur on their industry), but my education has been widened greatly by this book, for example I now understand how a positron camera works (and how many encounter those every day!).

The first edition of the book was entitled *Principles of Measurement for Anaesthetists* and aimed to acquaint the anaesthetist with the basic principles of measurement techniques which could be applied in his clinical practice. Now, however, the authors tell us such expertise has extended, both in content and its scope in application of medicine, so that their book is now encompassing measurement techniques employed by the cardiologists, respiratory physiologists, as well as the anaesthetists for whom they originally wrote. Surgeons, physicians, paediatricians and obstetricians are now included within the scientific community for whom this book is intended.

The first part, on general principles and instruments, covers units of measurement, basic mathematical concepts, and a daunting chapter on simple electronics, which convinces this reviewer that dabbling in this mystique really does justify the existence of medical physics departments. Biological potentials, data processing, optics and ultrasound lead on to radio-activity and finally patient safety. The second part of the book deals with specific measurements, including an excellent chapter on the measurement of pressure by both invasive and non-invasive methods, and clear descriptions of principles of operation of gas analysers, but in comparison a rather paltry treatment of respiratory physiology. The book concludes with two chapters on statistics, along with appendices including statistical tables.

Inevitably, this width of coverage, even in 300 pages, must dissatisfy any specialist, who feels that his particular interest has not been adequately treated. Nonetheless, most chapters conclude with a reasonably up-to-date 'suggestions for further reading', which I feel is essential for the many who will use this as a book of reference, for although it may be a required text for higher qualifications in anaesthesia, most physicians (and I suspect many surgeons) will be relieved to know that their College examiners have not yet discovered that it contains essential material for safe practice of today's medicine in their particular specialty.

For those who are not anaesthetists, who from the authors' preface need to know every word of this text to pass their higher examinations, this book will serve a major function in allowing the clinician to conduct a reasonably comprehensible conversation with his colleagues in medical physics, bioengineering, and indeed computing, and in this respect alone the book fulfills a very valuable function. A few such clinicians may feel it essential to own a personal copy, but there is no doubt that it will make a valuable contribution to any medical library, and could serve a useful role also nearer to the interface between patient and machine, as in the library of an intensive care unit, respiratory function laboratory, cardiac catheterization laboratory and possibly the coronary care unit. Any department with a research interest in application of physiological measurements to clinical practice would find this a valuable source of reference, and the clarity of the diagrams may even pursuade some of our essentially anumerate profession that mathematical concepts are not really beyond them. Clearly the first edition met the need, and I am sure this second edition does indeed justify its authors' expectations of informing a wider audience. The reviewer will use his copy frequently, to advice particularly new Research Fellows starting projects in applied respiratory physiology. However, I fear that it will soon be stolen, when the Fellows find out how useful it is.

It is a good book, possibly for a limited market, and for those outside anaesthesia (who appear to require to read it to pass their examinations), mainly for reference.

D. C. Flenley

Respiratory Diseases

John Crofton and Andrew Douglas

Oxford: Blackwell Scientific. 1981. Third Edition. P. xvi + 819. Price £35.00

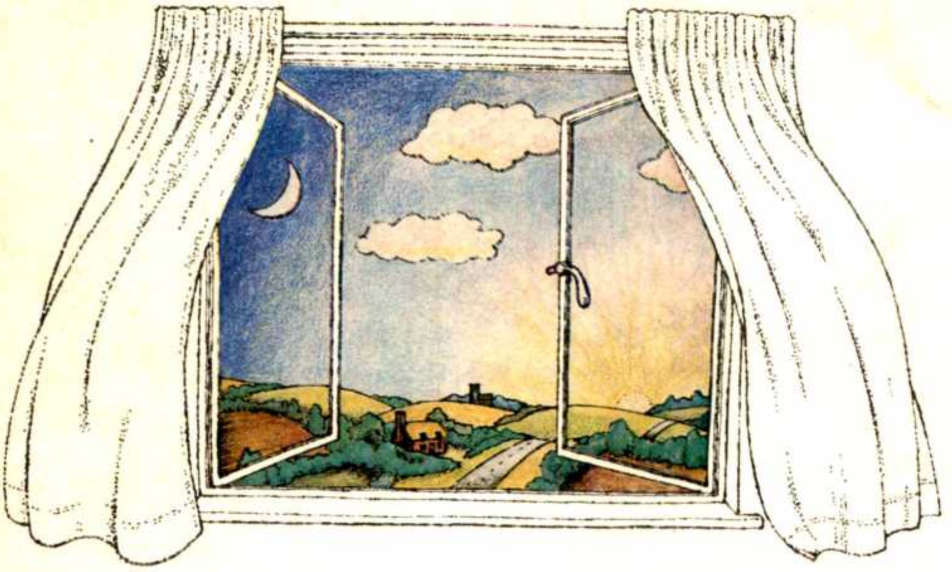
Visually, the third edition of this, the major British text book of respiratory disease, has changed for the worse in colour and shape, though the new wider format does make for easier reading and has allowed an only minimal increase in thickness. The line diagrams of chest X-ray appearances and the author index have been removed without serious loss and room has been found for important new chapters on congenital abnormalities, pulmonary oedema and pulmonary angiitis and granulomatosis. Otherwise the contents are much as before, though revised, and the arrangement of the chapters has improbably achieved even greater idiosyncracy than previously, with asthma separated from the other obstructive syndromes of chronic bronchitis and emphysema, and with bronchiectasis sandwiched between respiratory failure and pulmonary syphilis. That such technical details should be mentioned at all reflects the basic soundness of the book which remains an invaluable source of information on all aspects of respiratory disease. While concentrating, rightly, on local experience of disease, it is far from parochial and provides good comparative coverage of different conditions in different parts of the world. The authors have retained a major section on tuberculosis, for which they are to be congratulated: as survivors of the pre- and early chemotherapy eras they have unrivalled experience of the natural history of the disease which younger chest physicians cannot hope to gain personally.

The early chapter on lung function is rather fragmented and difficult to follow, with apparently randomly arranged sections on lung mechanics, gas exchange and blood gases, and a more orderly account with less emphasis on tests of nitrogen mixing such as closing volume would be desirable. Conversely, it would be helpful to the practising chest physician to have a fuller and more reasoned assessment of the role and value of specific lung function tests, rather than the perfunctory account given here.

However, on the content of the clinical chapters, it is hard to fault the new edition. Major respiratory problems such as asthma, chronic bronchitis, bronchial carcinoma and sarcoidosis are very well covered, with full and up-to-date references. Rarer lung diseases are succinctly described, again with adequate references to original texts, and the list of topics covered appears to be comprehensive. It is a pity that no space has been found for reproductions of some representative radiographs and histology, but presumably the cost would have been prohibitive.

In general then, this edition is a worthy successor to its excellent predecessors and reflects not only the wide knowledge and experience of the authors, but also their balanced and thoughtful approach to respiratory diseases and their treatment. It is an essential for the chest physician and the general physician will find it an invaluable guide to a large part of his practice, while even the undergraduate will benefit from selective reading.

G. M. Sterling



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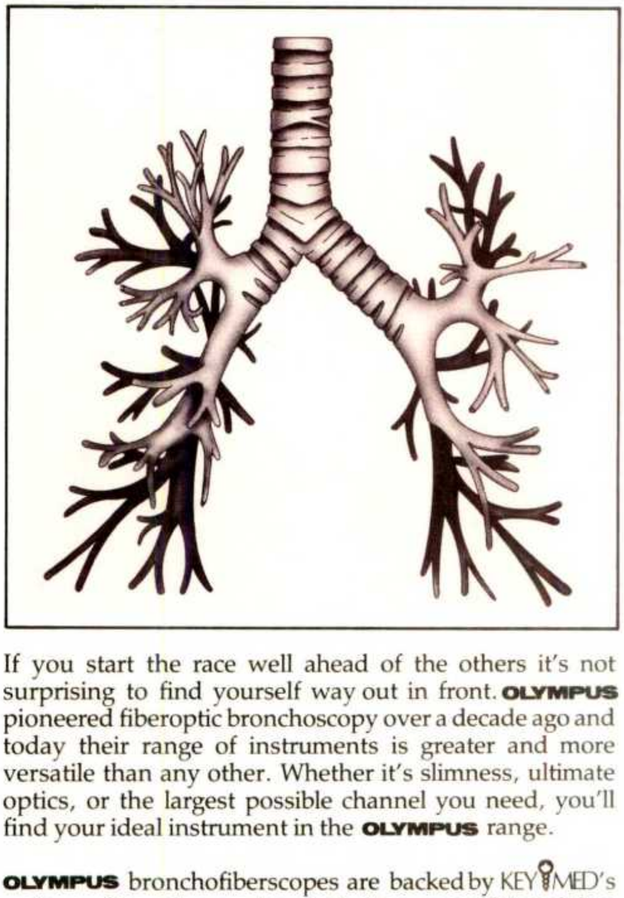

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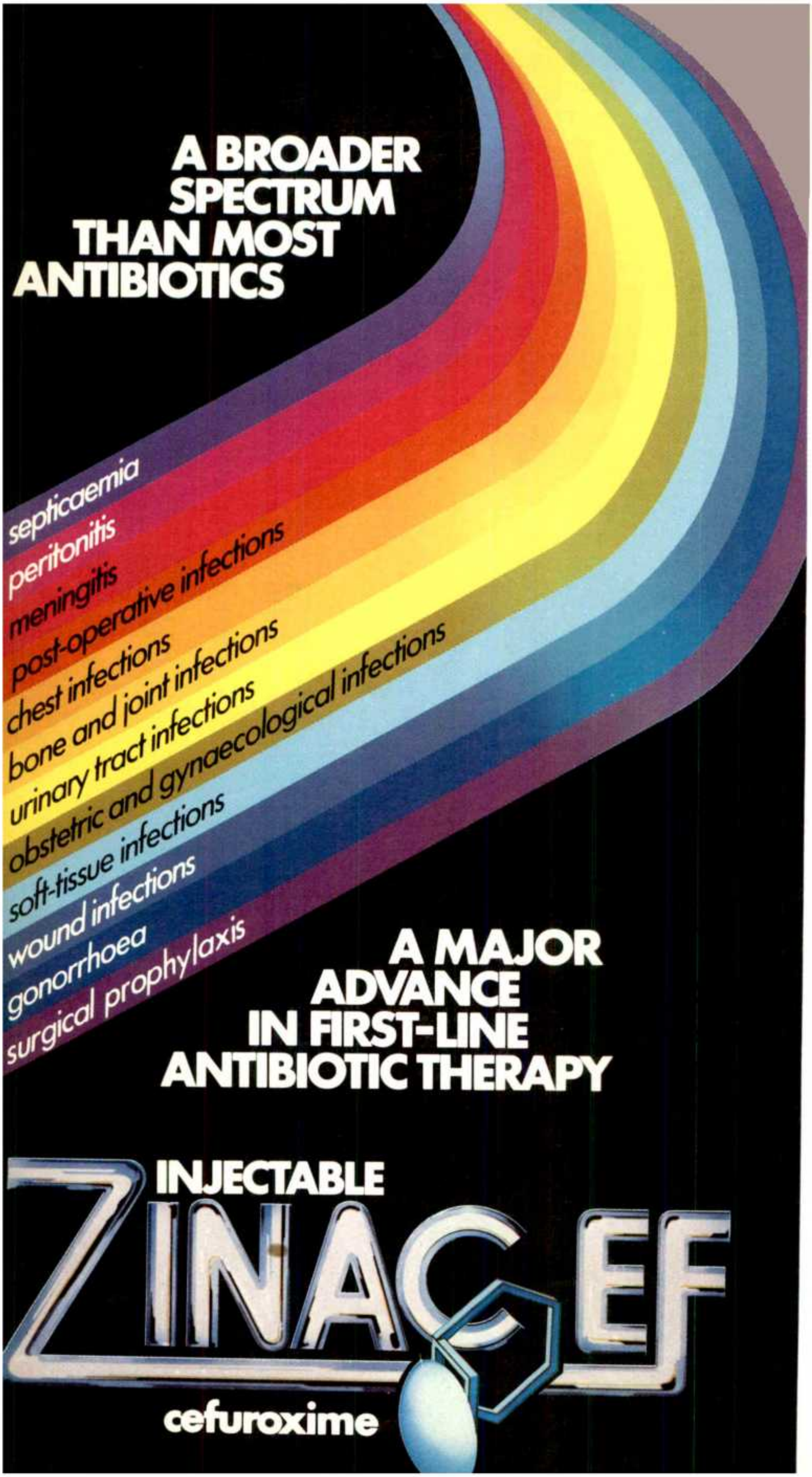
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COMPUTED TOMOGRAPHY OF THE THORAX IN THE DIAGNOSIS AND MANAGEMENT OF MALIGNANT DISEASE

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Summary

The role of computed tomography (CT) scanning in the investigation of patients with intrathoracic malignancy has not yet been clearly defined. Current evidence suggests that it is the most sensitive diagnostic radiological imaging technique for identifying the extent of primary lung cancers and their relationship to intrathoracic anatomy. It is an advance in the staging of intrathoracic malignancy as it identifies adenopathy in the paratracheal region and the mediastinum more readily. Discovery of small (< 0.8 mm) pulmonary nodules is common in patients with some extrathoracic malignant conditions, but differentiating malignant deposits from benign nodules remains a problem. CT has a potential place in radiotherapy field planning and in identifying lung cancers in the occasional patient presenting with suspicious symptoms or positive cytology and a normal chest radiograph.

Introduction

Computed tomography (CT) scanning was introduced as a diagnostic imaging tool in 1972. It has proved to be a major technical advance and has complemented the investigation of most major organ systems, often making invasive techniques redundant. Although it is increasingly used in the assessment of intrathoracic disease its place in the investigation of common respiratory conditions has not yet become clearly defined. This is probably due to the lack of general availability of CT scan units in the United Kingdom and the relative paucity of diagnostic studies comparing CT to better-established methods of investigation of lung disease. Conventional radiography of the chest is a simple procedure which produces results of high quality but suffers from a fundamental limitation in that it attempts to depict three-dimensional space on a two-dimensional film. Attempts to isolate a slice of tissue within the chest by conventional tomography are not entirely satisfactory in that shadows outside the slice, although blurred, are not completely eliminated. Furthermore, an X-ray film although able to detect marked density differences such as occur between blood vessels and aerated lung is quite unable to detect the very small density differences which occur within soft tissue. Hounsfield's (1972) discovery of computed tomography with its ability to distinguish previously undetectable differences of density and to visualize a well demarcated slice in a transverse plane can produce information in the lung, the mediastinum and the chest wall which is not obtainable by any other imaging technique.

The basic principle of computed tomography is the reconstruction of the internal structure of an object from multiple projections. In essence, the system consists of an X-ray tube mounted on a moving D-shaped frame with an array of X-ray detectors accurately positioned diametrically opposite the X-ray source. The movements of the tube-detector frame around the patient varies, the most widely used being a combination of traversing and rotatory movements. In this type the scanner frame with its X-ray tube and detectors traverses across the patient. At the end of each linear traverse the scanner frame with its tube and detectors rotates through an arc of 10 degrees and another linear traverse is then performed (Fig. 1). This process of traversing and 10 degree indexing continues until 18 traverses spanning 180 degrees have been completed. During each traverse the quantity of X-rays entering the patient is measured by a pre-patient detector and the quantity emerging from the patient is measured by the detector array. The absorption of the X-ray beam as it passes through the tissues can therefore be calculated, this X-ray attenuation being directly proportional to the absorption values of the tissues in the path of the X-ray beam. Over 300 000 absorption values taken during each scan are fed into a computer for analysis by a mathematical algorithm and reconstructed as a cross-sectional tomographic image.

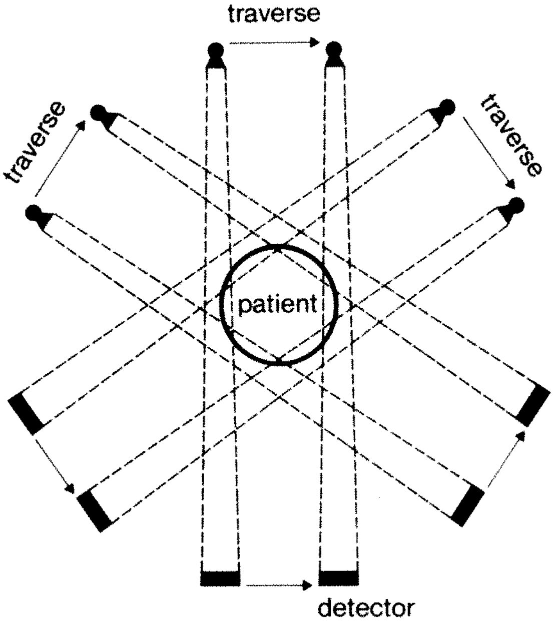

Fig. 1. Diagram to show the relation of the patient to the scanner movement

The absorption values obtained are given a CT value varying from +500 to

– 500 EMI units (+ 1000 to – 1000 Hounsfield (H) units). On this scale water is given a value of 0, dense bone + 500 and air – 500. The CT image may then be presented as a paper printout of CT numbers or as a visual image on a cathode ray tube.

When viewed as a visual image the digital results are converted to a grey scale but the eye cannot perceive the very small density differences which occur within such a wide range. The density differences i.e. the contrast of the image may be greatly increased by narrowing the range of CT values (window width) from black to white on the grey scale and the centre of the grey scale band (the window level) selected by the window width control may be moved up or down the scale of CT values. The ability to manipulate the density differences in this manner sets CT apart from any other imaging technique (Fig. 2) and it will be appreciated that the film selected by the investigator represents only a small fraction of the information contained within each transverse slice.

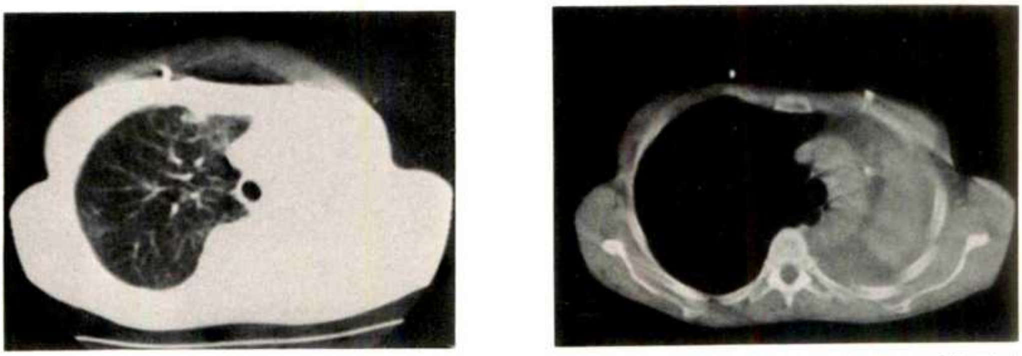

Fig. 2. The effect of changes in window level. *Left.* Level – 360. Aerated right lung. The left hemithorax is opaque with no visible detail. *Right.* Level + 40. The aortic arch, pleural effusion and a collapsed left lung is seen

The densities recorded represent the X-ray attenuations of all the structures within the slice and unless the structure occupies the whole slice thickness the measured attenuations will not represent the true attenuation value of that structure but will include a contribution from adjacent tissue (Fig. 3). This 'partial volume' effect can therefore produce misleading results, and respiratory movement imposes further limitations on the accuracy of density measurements, when the scanning time exceeds the patient's breath-holding capacity. These sources of error are minimized in the newer generations of scanners which offer much shorter exposure times and a variable slice thickness (2–13 mm).

Major areas of cancer management where CT has vital roles to play are the planning of radiotherapy fields, the identification of pulmonary metastases, the investigation of the mediastinum and the staging of lung cancer. This article reviews the available information and discusses the potential of CT scanning in the diagnosis and management of intrathoracic malignancy and in lung cancer in particular.

Clinical applications

Conventional radiography and tomographic techniques have served well for the initial evaluation of patients with chest disease. For this reason CT of the thorax has developed less rapidly than it has for the brain, where invasive techniques can now largely be avoided, and for the abdomen where alternative techniques are less successful. Most of the CT literature on the thorax is confined to the diagnosis and management of pulmonary nodules. However, CT should ideally become an essential procedure in the investigation of lung cancer because of its value in assessing mediastinal involvement by tumour and peripheral spread of the disease to the chest wall, as well as its ability to demonstrate remote metastases particularly in the adrenals, the liver and kidneys.

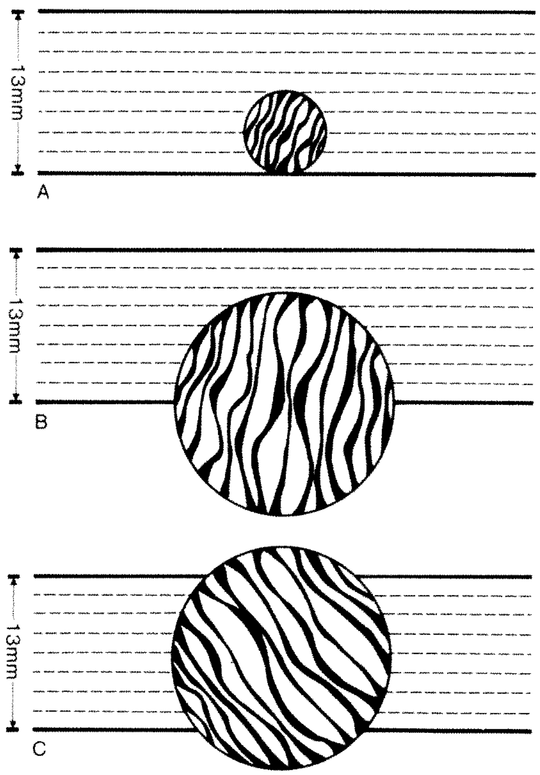

Fig. 3. Diagram of 'partial volume' effect in a conventional 13 mm slice. (a) Small lesion causing a falsely low attenuation value. (b) Lesion larger than 13 mm but not completely in slice causing falsely low attenuation value. (c) Lesion filling whole slice – true attenuation value

CT scanning in the staging of lung cancer

Using the TNM classification of extent of disease (Mountain et al. 1974), CT scans of the thorax have been shown to worsen disease staging in 40% of patients with

Table I. Change in T status after CT scanning in 50 patients with small-cell carcinoma of the lung (from Harper et al. 1981)

T stage	*Conventional staging*	*CT staging*		
		T1	T2	T3
T1	3	–	–	3
T2	32	–	8	24
T3	15	–	–	15

non-small-cell cancer (Emami et al. 1978) and in 77% of patients with small-cell lung cancer (Harper et al. 1981). Both these studies demonstrated that CT was particularly successful in detecting mediastinal lymphadenopathy (although not all patients had mediastinal tomography), and in visualizing extension of the tumour towards the pleural cavity and to the thoracic bony cage. However studies which have compared conventional tomography with CT scanning have shown the latter to be superior, particularly for detecting mediastinal lymphadenopathy and pleura involvement (Lackner et al. 1979; Mintzer et al. 1979).

In 32 patients with non-small-cell lung cancer studied primarily to assess the influence of CT on radiotherapy field planning (Emami et al. 1978), the tumour was more clearly delineated in 75% of patients when compared with the plain chest radiograph. Thirty-two areas of involvement by tumour not suggested by other data were identified in 21 patients. In eleven patients direct extension of tumour to bone and pleural surface were recognized. Unsuspected nodes were seen in nine patients (seven mediastinal, two hilar), while other areas of tumour involvement were also noticed in six (lower neck, bone, pleural effusion). Using the TNM classification the tumour (T) staging was increased in fourteen of the 32 patients and the nodal (N) stage was increased in nine.

In our study of 50 consecutive patients presenting with small-cell carcinoma of the lung a cell type recognized to be most aggressive and to disseminate much earlier than other lung cancers, CT again provided much additional information (Harper et al. 1981). By conventional staging 70% of the patients were thought to have a T1 or T2 (localized) tumour, the remaining 30% being classified as T3 (extensive) tumours. Following CT scans 77% of the seemingly localized tumours were found to be T3 including all three T1 tumours (Table I). The reclassification

Table II. Detection of direct tumour extension by CT scanning in 50 patients with small-cell carcinoma of the lung (from Harper et al. 1981)

	Conventional staging (No. of cases, %)	*CT staging* (No. of cases, %)
Pleura	3	17
Mediastinum	8	20
Diaphragm	0	1
Total	11 (22%)	38 (74%)

Table III. Sites of lymph node involvement within the thorax in 50 patients with small-cell carcinoma of the lung (from Harper et al. 1981*a*)

Lymph node group	*Conventional staging*		*CT staging*	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Paratracheal	11	8	16	9
Carinal	1	0	16	0
Hilum	38	1	38	2

as T3 was due to finding direct tumour extension into the adjacent structures of the mediastinum, pleura or diaphragm in 26 of the 27 cases and of a pleural effusion, subsequently shown to be malignant, in the remaining case (Table II). In all 15 cases which were conventionally classified as T3 the stage was confirmed by CT scans.

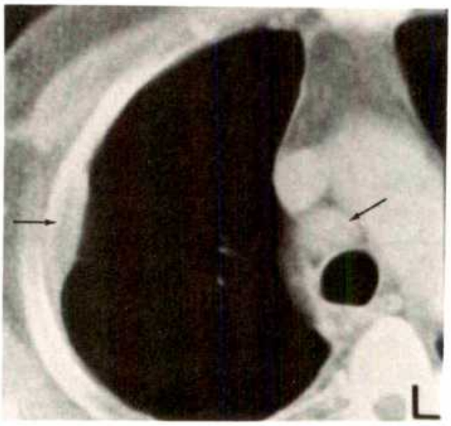

Fig. 4. Enlargement of right paratracheal gland. A peripheral deposit invading chest wall also seen (arrowed)

CT scans appear to add less to the identification of hilar lymphadenopathy as this is usually well seen on conventional radiography or on tomograms (Mintzer et al. 1979; Harper et al. 1981; Table III). However paratracheal enlargement is better identified with CT (Fig. 4), and an additional six cases with enlarged paratracheal glands were added to the 19 identified with conventional radiology in the 50 cases of small-cell carcinoma studied by Harper et al. (1981; Table III). The CT scan is clearly superior in the subcarinal region (Fig. 5), identifying 16 cases with enlarged subcarinal lymph nodes compared to one by conventional means, although only half of these patients had tomography of the mediastinum (Table III), thus considerably increasing the N status of patients (Table IV). Mintzer et al. (1979) compared conventional tomography of the mediastinum with CT scanning in 100 patients with chest malignancy and again showed CT to be superior in evaluating the mediastinum. CT identified abnormalities in 75% of patients subsequently found to have disease at thoracotomy, whilst conventional tomograms were either falsely negative or equivocal in 62.5% of cases. It would appear therefore that from the limited information compiled to date CT identifies mediastinal lymphadenopathy more readily and accurately than other available non-invasive techniques. This does not necessarily mean that CT scanning should be an alternative to mediastinal biopsy in patients considered candidates for operation. To date only one study has compared CT findings in the hilum and mediastinum to mediastinal biopsy in lung cancer. All lymphadenopathy considered due to metastatic spread by conventional techniques and by CT was confirmed by mediastinal biopsy, but one-third of the cases with lymph node involvement found at biopsy did not have this recognized by CT, a false negative rate of 28% (Underwood et al. 1979). Thus, on published evidence, CT scanning should not replace conventional invasive staging prior to thoracotomy. In those in whom lymphadenopathy is discovered to be reactive only, a finding associated with a better prognosis, the appearance is indistinguishable radiologically from enlargement due to tumour involvement. The subcarinal area which drains the lower lobe lymph vessels is beyond the range of conventional mediastinoscopy. Abnormalities here are best identified by CT scanning.

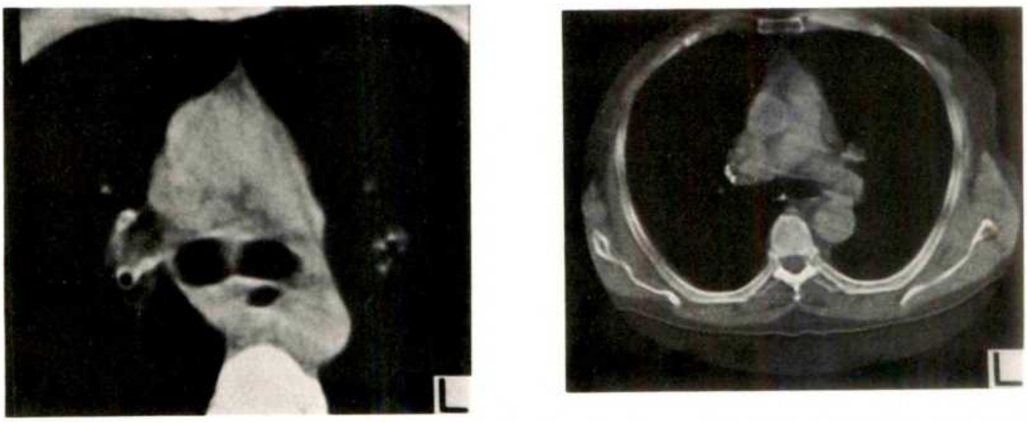

*Fig. 5. **Left.*** Slice at level of carina illustrating lymphadenopathy obliterating the subcarinal space. ***Right.*** Slice at similar level to show normal appearances

Table IV. Change in N status after CT scanning in 50 patients with small-cell carcinoma of the lung (from Harper et al. 1981)

N stage	*Conventional staging*	*CT staging*		
		N0	N1	N2
N0	5	2	2	1
N1	26		13	13
N2	19			19

The mediastinum

The cross-sectional images produced by CT are ideally suited to the study of the mediastinum, avoiding the superimposition of mediastinal structures inevitable with all other imaging techniques, and the improved density discrimination of CT distinguishes between vascular shadows, fat and solid tumour (Livesay et al. 1979). Density discrimination between blood vessels and other mediastinal structures is further improved by the routine use of intravenous contrast media given in the form of an intravenous bolus followed by a slow infusion – preferably into an arm vein on the same side as the suspected lesion. The infusion, continued during the scanning procedure of the superior mediastinum, produces marked opacification of the superior vena cava and innominate veins and increased opacification of the pulmonary arteries, the aortic arch and its branches. This contrast enhancement identifies vascular structures clearly and increases diagnostic confidence particularly in the interpretation of paratracheal shadows. Comparative measurements of attenuation values before and after contrast enhancement may be of value in the investigation of suspected aneurysm and other vascular anomalies.

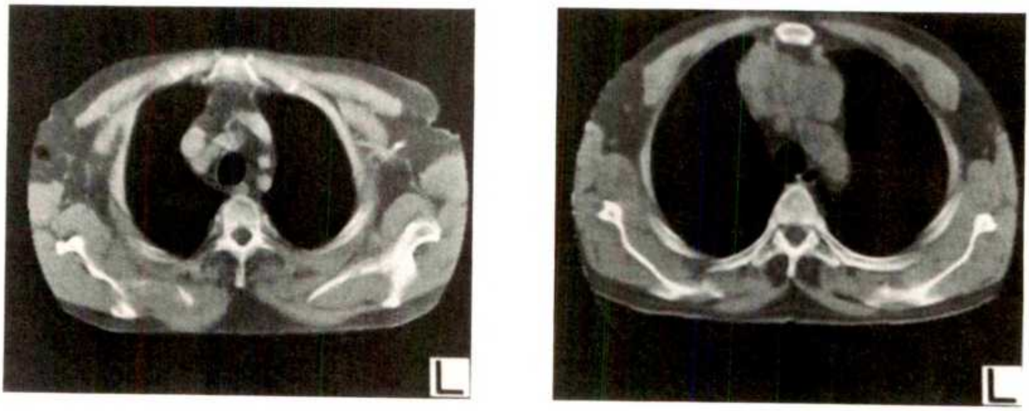

Fig. 6. Left. CT scan in patient with widened mediastinum on chest radiograph. Scan shows fatty infiltration by low attenuation tissue, the mediastinal vessels being clearly identified. *Right.* Similar problem: CT revealed high attenuation mass, subsequently shown to be a lymphoma

The demonstration of negative CT attenuation values permits definite identification of fatty lesions such as Morgagni herniae, pericardial fat pads, dermoid or simple accumulation of fat in the mediastinum due to obesity or steroids (Fig. 6). However, misleading results may be obtained with higher positive attenuation values as it may not be possible to differentiate with certainty between solid tumours and benign cysts containing viscid protein-rich fluid (Marvasti et al. 1981).

Occult thymoma in myasthenia gravis (Mink et al. 1978) and red cell aplasia may readily be demonstrated when standard radiographs and lateral tomograms are normal and the causes of widening of the paraspinal shadow clarified. Kreel

(1976) demonstrated lymph node enlargement by CT in eight of 14 patients with lymphoma, when it had not been seen by other radiological techniques including lymphangiography.

Radiotherapy planning

The available information suggests that CT is superior to conventional techniques for optimal planning. In 32 patients with non-small-cell lung cancer it allowed better delineation of the tumour extent in 24 patients, more accurate assessment of the size of the lesion in 14, more adequate coverage of tumour by radiotherapy portals in nine, and alterations in irradiated volume of normal tissue in 13 (Emami et al. 1978). Whole lung tomography was performed in only four of these patients and it can be argued that some of these findings might have been demonstrated by that technique. However in general, conventional tomography is 10–20% more accurate than plain chest films while in most studies CT was more 'helpful' than the information obtained from the plain chest radiograph in 75% of patients. In those few patients who have undergone both conventional tomography and CT in other studies additional information was provided in more than half the cases (Mintzer et al. 1979; Harper et al. 1981). It is clearly premature to suggest that CT planned radiotherapy improves the prognosis – though it is likely that a decrease in geographical misses of tumour will enhance the efficacy of radiotherapy treatment.

The three-dimensional detail possible with a CT has both allowed better identification of tumour masses and made it possible to measure tumour volume. Harper et al. (1982) have shown that tumour volume at presentation correlates inversely with prognosis in small-cell carcinoma of the lung treated by chemotherapy.

Pulmonary nodules

The detection of the solitary pulmonary nodule on a chest radiograph is a source of considerable concern especially in an asymptomatic patient. In a recent review (Siegelman et al. 1979) of five large series the most common diagnosis amongst 1711 resected nodules was granuloma 54% (a commoner finding in the United States than in Britain), lung cancer or other primary malignancy 28%, hamartoma 6.6%, metastases 3.5%, and bronchial adenoma 2%. Thus in the majority of American patients the lesions were benign and a thoracotomy was unnecessary. Steele (1963) showed the prognosis of patients with lung cancers presenting as solitary nodules under 2 cm in diameter was much better than those with larger lesions.

Attempts have been made to establish reliable radiological criteria for evaluating the solitary nodule. CT scanning identifies more pulmonary nodules than the plain chest radiograph and whole lung tomography, and this has added to the difficulty. Although conventional tomography is superior to a plain radiograph it underestimates the number of parenchymal nodules eventually found at thoracotomy in 30–50% of patients (Neifeld et al. 1977; Sindelar et al. 1978).

The superiority of CT over conventional techniques in identifying small non-calcified nodules is due not only to its high sensitivity but also to its ability, because the sections are transverse, to demonstrate nodules at sites which are difficult to visualize by other means, e.g. the retrosternal space, the costophrenic sulci, the retrocardiac paramediastinal area and the subpleural region of the lung (Fig. 7).

Most studies on detection of pulmonary nodules have been performed on patients with an extrapulmonary primary malignancy. Muhm et al. (1978) studied 91 patients, in 32 of whom CT detected more nodules than tomography. Thirty-one patients had resection of some or all of their nodules and in 27 patients the nodules were malignant. Bilateral nodules were detected in 13 patients in whom whole lung tomography had identified nodules in one lung only.

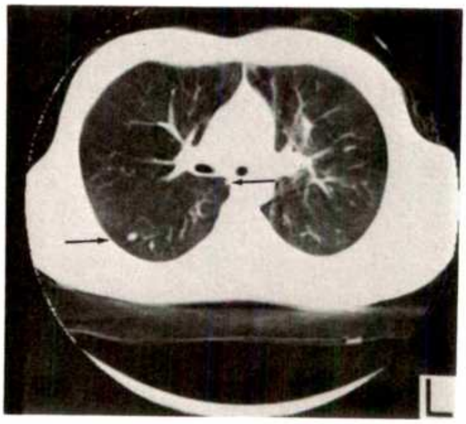

Fig. 7. Two pulmonary nodules not seen on plain radiograph in a patient with testicular teratoma. One subpleural beneath carina, the other in apex of right lower lobe

Schaner et al. (1978) compared conventional tomography with CT in 25 patients with extrathoracic primary malignancy (Ewing's sarcoma, rhabdomyosarcoma, fibrosarcoma and melanoma), in whom conventional tomography had revealed from one to four nodules in one lung which seemed to be resectable. Plain chest radiographs detected 21 nodules, tomography 38 and CT 69. Not all of these nodules were found at thoracotomy, but 19 of the 21 detected on the plain radiograph proved to be metastases (90%) with a median diameter of 17 mm. Eleven of the additional nodules seen on tomography were found of which six were malignant, with a median diameter of 7 mm. Of the 69 nodules identified with CT 47 were found at surgery – median diameter 4.5 mm. Fifteen of these nodules were identified by CT alone and only six were malignant – the other nine being granulomata or pleural based lymph nodes. An additional 45 nodules were not identified by any technique and were removed at thoracotomy (mean diameter 3 mm) and 15 were metastases. This study indicates that CT demonstrates more malignant nodules than tomography but associated with this is an increased rate of detection of nodules which subsequently prove to be benign. Nevertheless in conditions where pulmonary metastatic nodules occur commonly, e.g. testicular malignancy, CT increases the detection rate by about 20% over plain films and has replaced whole lung tomograms (Husband et al. 1981).

Although the presence of calcification in a nodule is said to indicate benign causes, the trap of scar cancers still remains, and the value of CT in the demonstration of calcification merits further investigation. Partial volume averaging interferes with accurate measurement of attenuation values and very small areas of calcification a few millimetres in diameter may escape detection although visible on conventional radiography, whereas larger, less densely calcified areas may be demonstrated when not seen on conventional radiography.

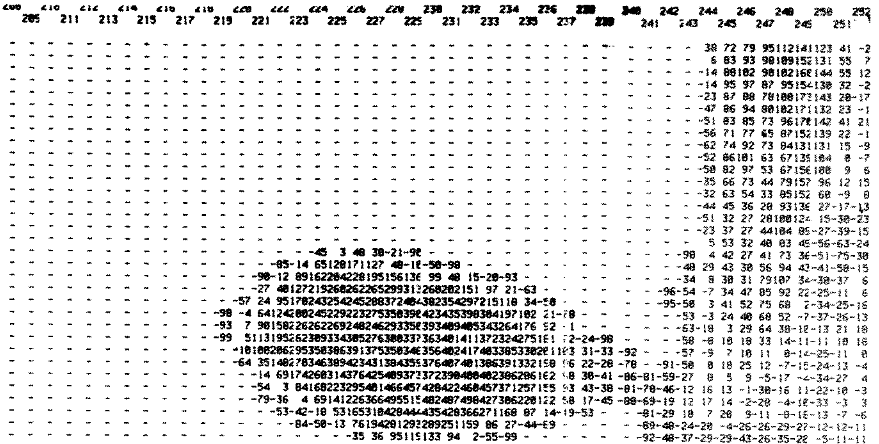

Fig. 8. **Digital printout of asymptomatic 2 cm nodule in left upper lobe of 56-year-old heavy smoker. The very high attenuation values are diagnostic of specks of calcification**

A useful approach to the management of patients with small nodules has been developed by Siegelman et al. (1980). They identified 91 apparently non-calcified pulmonary nodules in 88 patients whose lesions were initially detected on routine chest radiographs. Criteria for inclusion in the study were a nodule of any size in the lung parenchyma detected on plain chest radiograph, an earlier film having shown no nodule, in patients older than 30 years without a known malignancy; or patients of any age with known extrathoracic malignancy when standard tomography had failed to show any evidence of calcification. The nodule sizes on CT ranged from 4 mm to greater than 4 cm. After identifying the nodule on routine CT scans the patients were very carefully rescanned, breath-holding at functional residual capacity with scan thicknesses of 0.5 cm (for nodules of 1 cm or more) down to 2 mm for smaller lesions. The CT number of the nodule was determined and there was a clear-cut difference between the malignant and benign lesions, irrespective of the type of malignancy or cell type of a particular tumour. The malignant lesions had a mean CT number of 98H (13 lesions), whereas 24 of 33 benign lesions had CT numbers in excess of 147H, with only nine overlapping the malignant range. Twelve other calcified nodules had CT numbers greater than 600H. An example of the use of digital mapping is shown in Fig. 8.

Conclusions

CT scanning appears to be an important step forward in the identification and localization of abnormal masses within the thorax. Although it will readily identify such phenomena as alterations in vascular supply in the lung, parenchymal disease such as emphysema or fibrosis and pleural disease such as asbestos plaques, its most important current application appears to be in the staging of malignant disease. It offers a considerable advance in defining intrathoracic anatomy, but is clearly less valuable for predicting histology although the H value may offer a potential for improved precision in the future. The more precise identification of tumour within the lung and/or metastatic spread to the mediastinum is likely to reduce the number of thoracotomies. This is valuable because patients who undergo thoracotomy without resection frequently run a worse subsequent course than those with similar disease status who avoid surgery. At present it appears that CT provides the best available visualization of the mediastinum and may influence the decision on mediastinal biopsy. The important subcarinal area, beyond mediastinoscopy range, deserves special study. In our view, CT should therefore become a mandatory preoperative investigation in lung cancer.

The identification of small nodules in the lungs of patients with a primary lung cancer or with a resectable extrathoracic malignancy remains a problem, but accurate determination of the CT numbers in thin slice scans may be valuable.

The presence of a pulmonary nodule will influence treatment of a malignant disease and the indications for a CT thorax scan proposed by Isherwood and Best (1980) seem appropriate:

1. A patient with a highly malignant tumour such as a sarcoma in whom the detection of a pulmonary metastases may contraindicate surgery.

2. A patient with a known extrathoracic tumour and a solitary nodule in the lung, in whom CT may exclude additional nodules and allow surgical resection.

3. A patient with a known malignant disease who would benefit from additional treatment to pulmonary metastases if these were detected.

In lung cancer the identification of nodules in the ipsilateral lung during staging appears important as they could be excised if not contained in the specimen resected when removing the primary. If nodules were detected in the contralateral lung management becomes more difficult and much would depend on the appearance and size of the nodule on CT. Again, further studies are urgently needed.

Another use of CT is in detecting occult disease in patients presenting with haemoptysis and a normal chest radiograph and bronchoscopy. Occasionally CT will demonstrate abnormalities such as bronchiectasis or, more dramatically, a carcinoma (Fig. 9).

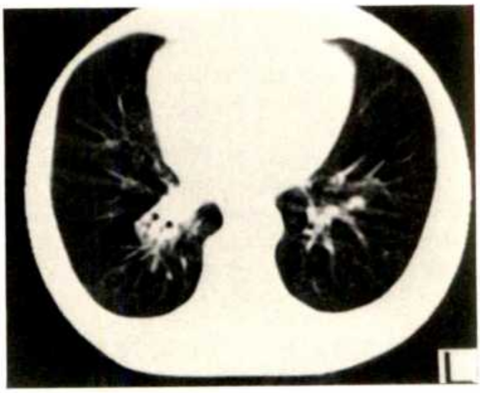

Fig. 9. Carcinoma in right lower lobe of male patient, heavy smoker, presenting with haemoptysis; chest radiograph and bronchoscopy were normal

Thus the current major indications of CT scanning may be summarized:

1. Preoperative assessment of lung cancer.
2. Screening of patients with normal conventional radiographs with extrapulmonary malignant disease which commonly metastasizes to the lungs.
3. Screening of a patient in whom the resection of a lung metastasis is planned.
4. Investigation of mediastinal masses.

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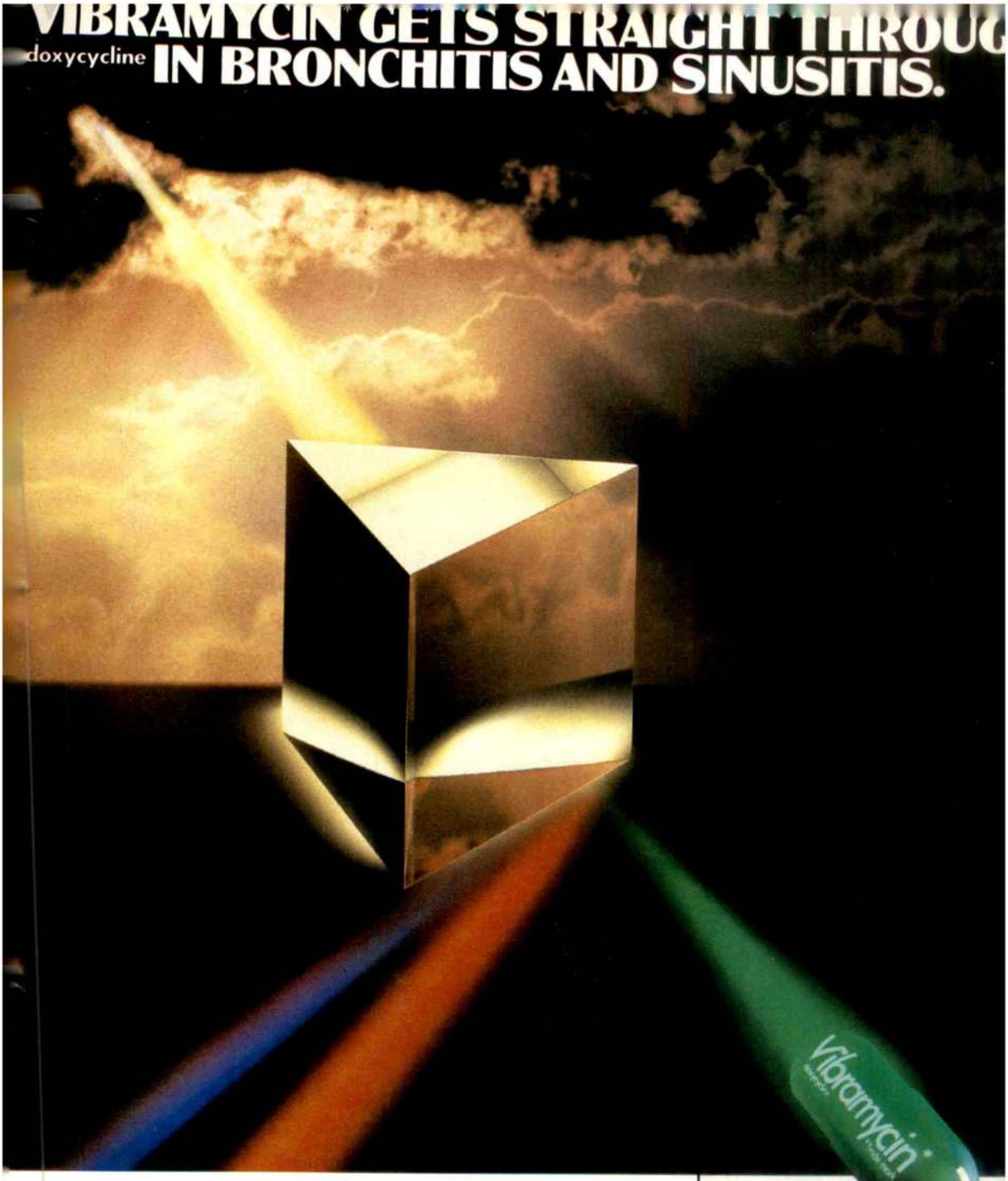

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norning bronchospasm
- As prophylaxis against
xercise-induced asthma
- As a rescue device
or control of breakthrough
ronchospasm

Routine use

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more frequent
- For chronic asthmatics
requiring regular bronchodilat
therapy to maximise lung
function
- In more severe asthma wher
specific anti-inflammatory
therapy (e.g., Becotide Inhaler)
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or emphysema responsive
to bronchodilator therapy

INHALED Ventolin

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utine control of bronchospasm in bronchial asthma,
tis and emphysema, or as required to relieve attacks of
onchospasm. Doses may also be taken before exertion to
exercise-induced asthma or before exposure to a known
able challenge.
and administration As single doses for the relief of
onchospasm, for managing intermittent episodes of
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entolin Inhaler – *Adults:* one or two inhalations.
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entolin Inhaler – *Adults:* two inhalations three or four
day. *Children:* one inhalation three or four times a day
to two inhalations if necessary.

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Precautions If a previously effective dose of inhaled Ventolin fails to give relief lasting at least three hours, the patient should be advised to seek medical advice. Ventolin should be administered cautiously to patients suffering from thyrotoxicosis. Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.

Side effects No important side effects have been reported following treatment with inhaled Ventolin.

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of the stated amount of microfine Salbutamol BP (as sulph
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Basic NHS cost 78p.

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Ventolin Inhaler	0045/5022
Ventolin Rotacaps 200mcg	0045/0116
Ventolin Rotacaps 400mcg	0045/0117

Br. J. Dis. Chest (1982) 76, 223

THE IMPORTANCE OF AEROSOL TECHNIQUE: DOES SPEED OF INHALATION MATTER?

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Summary

Using a simple timing technique patients were taught to inhale an aerosol of β_2-agonist bronchodilator at a rate of about 0.5 litre/second. The bronchodilator response was compared to that produced by an inhalation speed of about 2.0 litres/second. With the inhaler held at the level of the open lips and a breath-holding time of four seconds no difference in bronchodilator response could be shown for the different inhalation speeds for groups of patients with bronchial asthma and chronic bronchitis.

INTRODUCTION

Aerosols of β_2-agonists are widely used in the treatment of obstructive lung disease. Although the majority of the dose is deposited in the oropharynx, the bronchodilator effect is thought to be the result of agonist acting on β_2-receptors in the bronchial tree (Ruffin et al. 1978). The exact site of these receptors is unknown but may be in relation to peripheral airways (Hensley et al. 1978). Therefore, factors which increase the deposition of β_2-agonists in the bronchial tree or produce a more peripheral deposition might be predicted to result in a better bronchodilator response. Inertial impaction of the aerosol particle in the upper airways increases with increasing velocity of the air stream. With increasing flow velocity turbulent air flow may penetrate more deeply into the lung and cause more particle deposition on the walls of the proximal airways (Brain & Valberg 1979). It has been shown in patients with air flow obstruction by a radio-labelled particle technique that a slow inhalation speed produces more peripheral deposition (Pavia et al. 1977). In normal subjects increasing flow rate lessens the deposition of particles in the lung but increases the proportion deposited in larger airways (Dolovich et al. 1981).

This study was designed to examine whether a slow inhalation of β_2 aerosol by a technique that could easily be mastered by the patient produced a better bronchodilator response compared to a standard fast inhalation technique.

Patients and Methods

Sixteen patients with reversible airways obstruction were studied. All patients had been shown previously to have a greater than 15% increase in the forced expiratory volume in one second (FEV_1) following a 200 μg dose of inhaled fenoterol. Eight of these were felt to have chronic bronchitis, i.e. had a productive cough for in excess of three months a year for the previous two years. All of this group were either present smokers or ex-smokers. The other eight patients did not have a productive cough and were classified as suffering from bronchial asthma. Inhaled β_2-agonists were stopped at least eight hours before the test. Inhaled steroids and oral theophylline were taken at the same time on both days. No patient was on oral steroids.

Each patient was studied by a slow and a fast inhalation technique on consecutive days, the order being randomized. Tests were done at the same time of day on the two days. Base-line spirometry was carried out and measurements taken of FEV_1, forced vital capacity (FVC), and maximal mid expiratory flow rate (MMEF). Following base-line measurements the patients were given one puff (200 μg) of fenoterol and the measurements were repeated 30 minutes later. The inhaler was held at the level of the open mouth and was activated by the technician at the beginning of inspiration. The patients breathed in from residual volume and breath-holding time was four seconds after inhalation on both days. The time of inhalation was recorded to the nearest second. On the fast inhalation day the patients were instructed to take a rapid breath in. In most patients this took approximately one second. On the slow inhalation day the inhalation time was calculated to give a flow of about 0.5 litre/second based on the pre-bronchodilator VC. For example, a patient with a vital capacity of 3 litres would be timed to inhale over six seconds. The technicians trained the patient to inhale over this period of time with the use of a metronome. They repeated the slow inhalation several times until the patient had mastered the technique before using the aerosol.

Separate analyses of variance were performed on each of the three lung functions measured. Duncan's test was used to assess any difference between inhalation techniques in lung function, both pre and post inhalation. Paired t-tests were used to test the difference between days in absolute and percentage changes from base-line.

RESULTS

Details of inhalation times and lung function before and after fenoterol are shown in Tables I and II. For both asthmatic and bronchitic patients there was no significant difference between the two days in base-line lung function. Following inhalation of fenoterol in the asthmatic group there was significant increase in FEV_1 and FVC ($P < 0.01$) on both days and MMEF ($P < 0.05$) on both days. However, comparing the two inhalation techniques there was no difference in either absolute or percentage changes in FEV_1, FVC or MMEF. In the bronchitic group the increase in FVC and MMEF from base-line was significant on both days (FVC, $P < 0.01$ on fast day, $P < 0.05$ on slow day; MMEF, $P < 0.05$ on both days). The improvement in FEV_1 from base-line was significant on the slow day ($P < 0.05$) but just failed to reach significance on the fast day. Again comparing the improvement in lung function on the fast and slow days there was no significant difference in either absolute or percentage terms for FEV_1, FVC or MMEF.

Thus although both patient groups showed significant improvement in lung function following bronchodilator, it could not be shown that a fast or slow technique was superior.

DISCUSSION

Although the greater part of an inhaled aerosol is deposited in the oropharynx probably only that deposited in the bronchial tree produces significant bronchodilation (Ruffin et al. 1978). Relatively little is known about the deposition of pressurized aerosols in the respiratory tract. A recent study of patients with obstructive airway disease suggested that about 3% of the total dose was deposited in the alveoli and about 6% in the conduct-

Table I. Results in the asthma group

Patient	*Sex and age*	*Smoking*	*Concurrent medication**	*Inhalation time (sec)*			*Fast inhalation*			*Slow inhalation*		
				Fast	Slow		FEV$_1$ (litres)	FVC (litres)	MMEF (litres/sec)	FEV$_1$ (litres)	FVC (litres)	MMEF (litres/sec)
1	M, 29	Never	S, B	1	10	Pre-	3.2	5.0	2.15	3.4	5.0	2.6
						Post-	3.65	4.95	3.25	4.0	5.3	3.4
2	F, 49	Ex (2 years)	—	1	5	Pre-	1.8	2.35	1.2	1.65	2.6	1.3
						Post-	2.1	2.85	1.45	2.1	2.85	1.6
3	M, 19	Never	B	2	10	Pre-	3.15	4.9	2.1	3.2	4.95	2.05
						Post-	4.15	5.6	3.85	4.4	5.75	4.0
4	F, 49	Ex (15 years)	S, B	1	4	Pre-	1.0	2.2	0.4	1.0	1.9	0.55
						Post-	1.3	2.6	0.5	1.3	2.5	0.55
5	F, 47	Never	S, B, T	1	2	Pre-	0.75	1.9	0.35	0.7	2.0	0.25
						Post-	1.1	2.5	0.5	1.2	2.5	0.6
6	M, 49	Never	B, T	1	4	Pre-	0.8	1.65	0.45	0.7	1.8	0.35
						Post-	1.8	3.9	0.85	1.35	3.2	0.55
7	F, 55	Ex (3 years)	S, B	1	3	Pre-	0.75	1.5	0.3	0.8	1.6	0.3
						Post-	1.0	2.15	0.45	0.9	2.1	0.4
8	F, 48	Ex (10 years)	T, B	2	4	Pre-	1.1	1.95	0.6	1.2	1.9	0.65
						Post-	1.2	2.05	0.5	1.45	2.15	0.9

* S = inhaled steroid; B = inhaled β_2-agonist; T = oral theophylline.
Pre- = Pre-fenoterol; Post- = Post-fenoterol.

Table II. Results in the chronic bronchitis group

Patient	*Sex and age*	*Smoking*	*Concurrent medication**	*Inhalation time (sec)*			*Fast inhalation*			*Slow inhalation*		
				Fast	Slow		FEV_1 (litres)	FVC (litres)	MMEF (litres/sec)	FEV_1 (litres)	FVC (litres)	MMEF (litres/sec)
1	M, 69	Current	B, T	1	4	Pre-	0.8	2.2	0.3	0.95	2.05	0.35
						Post-	1.0	2.2	0.35	1.05	2.15	0.45
2	M, 54	Ex (9 years)	S, T, B	1	4	Pre-	0.55	1.8	0.25	0.5	1.75	0.25
						Post-	0.65	2.2	0.35	0.6	2.0	0.35
3	M, 69	Ex (4 years)	T, B	1	3	Pre-	0.5	1.5	0.2	0.5	1.5	0.2
						Post-	0.6	2.15	0.2	0.4	1.6	0.2
4	M, 74	Current	T, B	2	3	Pre-	0.5	1.4	0.15	0.4	1.5	0.15
						Post-	0.5	1.5	0.2	0.55	1.85	0.2
5	M, 64	Ex (6 years)	T, B	1	3	Pre-	0.7	1.9	0.2	0.7	1.8	0.25
						Post-	1.05	2.45	0.35	1.2	2.4	0.45
6	M, 65	Ex (1 year)	S, B	1	4	Pre-	0.4	1.9	0.25	0.4	2.0	0.3
						Post-	0.7	1.95	0.3	0.6	2.15	0.3
7	M, 64	Current	S, T, B	2	5	Pre-	1.0	3.15	0.35	0.9	3.25	0.3
						Post-	0.7	3.65	0.4	1.1	3.2	0.4
8	M, 62	Ex (12 years)	S, T, B	1	3	Pre-	0.5	1.35	0.2	0.45	1.5	0.2
						Post-	0.6	2.05	0.2	0.55	1.9	0.2

* S = inhaled steroid; B = inhaled β_2-agonist; T = oral theophylline.
Pre- = Pre-fenoterol; Post- = Post-fenoterol.

ing airways (Newman et al. 1981). The speed of inhalation should be important in determining distribution. With increasing velocity of air flow deposition in the proximal airways by impaction would be expected to increase (Brain & Valberg 1979). A study in patients with airflow obstruction using radio-labelled polystyrene particles (Pavia et al. 1977) showed an inverse relationship between speed of inhalation and alveolar deposition. In normal subjects increasing speed of inhalation decreased the total particle deposition in the lungs but increased the proportion deposited in large airways (Dolovich et al. 1981).

In this study an inhalation speed of about 0.5 litre/second was compared with that of approximately 2 litres/second. A speed of about 0.5 litre/second was chosen for the slow day as it was felt that this was easily manageable by the patients and had been suggested by previous studies to increase the dose deposited in the lungs compared to inhalation speeds of around 2 litres/second (Ryan et al. 1981).

In the usual clinical situation the site of air flow obstruction is not known with certainty in any given patient. The site of obstruction may vary with different stimuli to bronchoconstriction (McFadden & Ingram 1979). More peripheral obstruction may occur in patients who smoke or have chronic bronchitis (Antic & Macklem 1976) and in patients with more severe obstruction, particularly those with an FEV_1 of less than 1.2 litres (Fairshter & Wilson 1981).

In this study no advantage could be shown in a slow inhalation technique in patients with chronic bronchitis. All the patients in this group had an FEV_1 under 1.2 litres. The numbers were too small to draw definite conclusions related to smoking history, but no trend was apparent.

Thus this study failed to show that a manoeuvre which ought to have increased periphal deposition of aerosol produced any measurable improvement in bronchodilator response, even in those patients where peripheral obstruction might have been expected. Although there is little detailed information about the distribution of β_2-receptors in the human bronchial tree it is suggested that they may be in relation to peripheral airways in normal subjects (Hensley et al. 1978). Patients who have substantial small airway obstruction tend to respond to bronchodilator administration with small airway dilatation (Wilson & Fairshter 1979), again suggesting that there are receptors in relation to small airways.

These results differ from those reported by Newman et al. (1980) who showed significantly better bronchodilator response with a slow inhalation technique combined with a breath-holding time of 10 seconds. Apart from the influence of inhaler mouth position and breath-holding time, which differed in our respective studies, patient selection possibly influencing site of air flow obstruction may have explained the discrepancy between the two studies.

In this present study the method of timing was relatively crude and thus likely to be less accurate than the computerized system used by Newman et al. (1980). However, this technique was deliberately designed as one which a patient could manage on his own without the need for complicated apparatus.

A 200 μg dose of fenoterol was used as this is the dose produced by one puff of the standard aerosol and thus is the minimum dose used in clinical practice. It is possible, however, that this dose was sufficiently large to produce near maximal bronchodilation with both techniques and thus mask any small difference between the two techniques which might have been apparent if a smaller dose of bronchodilator had been used.

In summary a simple timing technique was used to produce a slow inhalation of a standard dose of bronchodilator aerosol. With the aerosol held at the level of the open mouth and a breath-holding time of four seconds no advantage could be shown compared to a rapid inhalation in patients with either bronchial asthma or chronic bronchitis.

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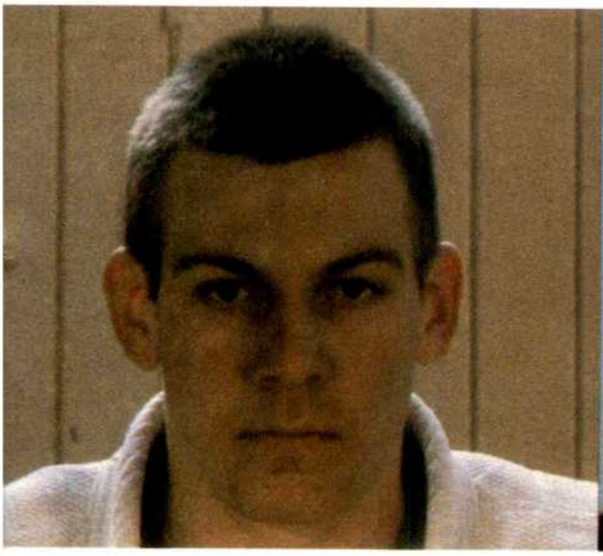

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PRESSURIZED BRONCHODILATOR AEROSOL TECHNIQUE: INFLUENCE OF BREATH-HOLDING TIME AND RELATIONSHIP OF INHALER TO THE MOUTH

P. LAWFORD AND D. MCKENZIE

Pulmonary Function Laboratory, University of Aberdeen

Summary

Twenty-seven patients with reversible airways obstruction have been studied to determine the effect of two methods of aerosol delivery on bronchodilator response to fenoterol.

There was no significant difference in response after inhaling with the mouth open or closed, and breath-holding for 10 seconds offered no significant advantage compared to 4 seconds.

Introduction

Despite the widespread use of pressurized aerosol bronchodilators in the treatment of airways obstruction, there is considerable doubt about the best method of administration of inhalers, in particular the position of the inhaler in relation to the mouth and the breath-holding pause at the end of inhalation (Newman et al. 1981). We describe two studies designed to elucidate these aspects of technique.

Patients and Methods

Both studies had the approval of the Hospital's Ethical Committee. Criteria for entry included a history of chronic or episodic wheeze, an initial FEV_1 less than 80% predicted, at least 15% increase in FEV_1 after two puffs isoprenaline or salbutamol, in patients who showed good synchronization of puff and breath.

Patients omitted bronchodilator therapy for 9 hours before each visit but continued oral or inhaled corticosteroid or cromoglycate. They attended the Pulmonary Function laboratory on four separate occasions a week apart at the same time of day. After resting, base-line (best of three) measurements of FEV_1, forced vital capacity (FVC) and peak expiratory flow (PEF) were made. Patients then received two puffs of fenoterol hydrobromide (200 μg per puff) or placebo from masked aerosol canisters according to a Latin square plan.

Study no. 1 – open versus closed mouth technique

Sixteen patients (10 males) of mean age 50 (20–73) took part in the first study. Thirteen were concurrently receiving inhaled and six oral corticosteroids and one was taking cromoglycate.

They inhaled aerosol with their usual inspiratory effort. On two of the four days the inhaler was placed in the mouth with lips applied to actuator and on the other days the actuator was held 3 cm away from the open mouth using a plastic frame. Inhalations were patient-activated at or near residual volume (RV), continued to total lung capacity (TLC), and the breath-holding time was 10 seconds.

Study no. 2 – breath-holding time

Eleven patients (6 males) of mean age 46 (17–60) took part in the second study. Nine were concurrently receiving inhaled and three oral corticosteroids and two were receiving cromoglycate. They inhaled 400 μg fenoterol hydrobromide or placebo at their usual inspiratory flow rate, from RV to TLC and then held the breath for either 4 or 10 seconds; time was monitored on the kymograph of a P.K. Morgan Resparameter. Simultaneous measurement of flow was made by placing the inhaler unit in series with the rolling seal spirometer of the Resparameter attached to a flow–volume differentiator and Bryans X-Y recorder.

For the purposes of calibration, peak inspiratory flow was compared against a Fleisch pneumotachygraph in 20 normal subjects; the correlation coefficient was 0.89.

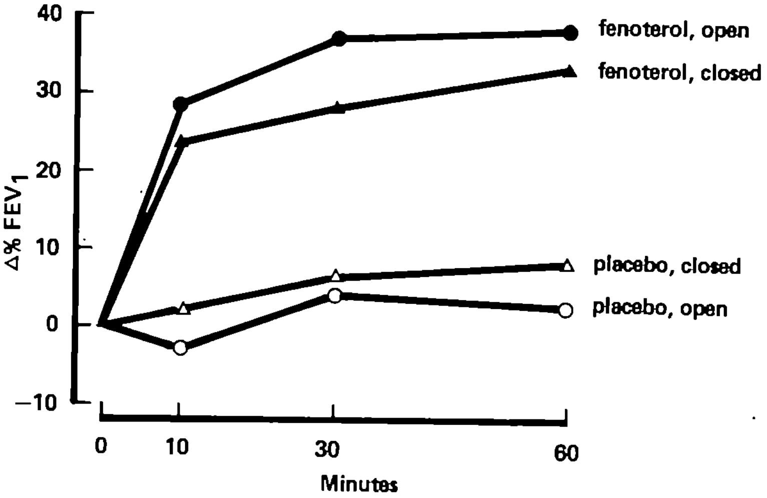
Subsequent measurements of FEV_1, FVC and PEF were made at 10, 30 and 60 minutes after administration of test aerosol and expressed as litres or millilitres, or litres per second, ATPS. The temperature of the laboratory was kept constant between 20 and 22°C throughout.

Statistical analysis of the significance of difference between means of absolute change was by paired *t*-test.

Results

Open versus closed mouth

Mean initial FEV_1 was 49.6% predicted and there was no significant difference in mean initial FEV_1 on any treatment day. The results are shown graphically in Fig. 1 as mean percent change in FEV_1, and in Table I as mean absolute change in FEV_1 at 10, 30 and 60 minutes. There was no significant difference in mean



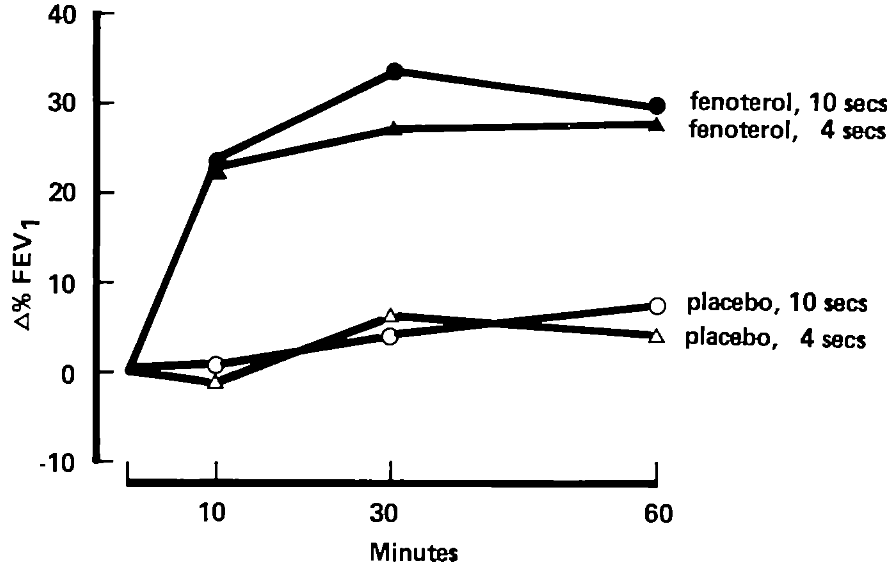
Mean percent change in FEV_1 at 10, 30 and 60 minutes after 400 μg Fenoterol hydrobromide or placebo, inhaling with closed (△) or open (○) mouth technique.

Fig. 1

Table I. Mean absolute change in FEV_1 (ml, ATPS ± 2 SE) at 10, 30 and 60 minutes after inhaling 400 μg fenoterol hydrobromide with lips applied to mouthpiece or with actuator held 3 cm from open mouth ($n = 16$)

	Closed	*Open*	*t*	*P*
10 min	306.2 ± 121.7	309.4 ± 130.8	−0.05	> 0.5
30 min	362.5 ± 119.0	368.75 ± 141.6	−0.08	> 0.5
60 min	425.0 ± 129.4	390.6 ± 148.4	0.52	> 0.5
10, 30 and 60 min	1093.7 ± 366.4	1068.75 ± 412.6	0.15	> 0.5

response after inhaling with the mouth closed as compared to inhaling with the aerosol 3 cm from an open mouth. Changes in FVC and PEF similarly showed no significant difference.



Mean percent change in FEV_1 at 10, 30 and 60 minutes after 400 μg fenoterol hydrobromide or placebo, when breath-holding time was 4 (△) or 10 (○) seconds

Fig. 2

Effect of breath-holding time

Mean initial FEV_1 was 46.0% predicted, and there was no difference in mean initial FEV_1 or mean inspiratory flow rate (about 2 litres/second) on any treatment day. Mean breath-holding times were 4.175 seconds and 10.0 seconds respectively.

Fig. 2 shows mean percent change in FEV_1 and Table II mean absolute change in FEV_1 at 10, 30 and 60 minutes. The difference in response after breath-holding

Table II. Mean absolute change in FEV_1 (ml ATPS ± 2 SE) at 10, 30 and 60 minutes after inhaling 400 μg fenoterol hydrobromide, breath-holding for 4 or 10 seconds ($n = 11$)

	4 sec	*10 sec*	*t*	*P*
10 min	209.1 ± 127.1	231.8 ± 132.3	−0.47	> 0.5
30 min	254.4 ± 138.5	281.8 ± 165.8	−0.5	> 0.5
60 min	268.2 ± 149.7	309.1 ± 164.5	−0.64	> 0.5
10, 30 and 60 min	722.7 ± 406.25	822.7 ± 454.8	−0.55	> 0.5

for 4 compared to 10 seconds did not reach statistical significance at the 5% level. Similarly there were no significant differences in response for FVC or PEF.

Discussion

Although Connolly (1975) showed significantly greater response in peak flow when isoprenaline was inhaled 4 cm from the open mouth compared to inhalation with the mouth closed, no subsequent work has confirmed this observation. Newman et al. (1981) showed no difference in response in eight asthmatics using terbutaline, and Dyson (personal communication) failed to show a significant difference in response to rimiterol using either a closed mouth or varying distances up to 4 cm from the open mouth. Despite using a different bronchodilator (fenoterol) and higher inspiratory flow rates than Newman et al., our study confirms the lack of benefit of the open mouth technique. Some patients, however, may prefer to use their inhaler in this way and although there is no evidence of a significant diminution of response, some aerosol may escape being inhaled.

Newman et al. are the only workers previously to have studied the effect of breath-holding time on bronchodilator response. Using an inspiratory flow rate of 25 litres/minute they showed that inhaled terbutaline produced significantly greater bronchodilatation, with a 10-second compared to a 4-second breath-holding pause (Newman et al. 1979), but a later study employing an inspiratory flow rate of 80 litres/minute showed no difference in response when the same breath-holding times were compared (Newman et al. 1980). Our study employed mean inspiratory flow rates slightly greater than this (118 compared to 80 litres/minute) and showed no difference significant at the 5% level between the two periods of breath-holding. At these flow rates, inertial impaction appears to be a greater determinant of maximum aerosol deposition than gravitational sedimentation (Stuart 1973).

Instruction leaflets accompanying aerosol bronchodilators advise that the inhaler should be used with lips applied to the mouthpiece, and that after inhalation the breath should be held 'for a few seconds'. This would seem to be sound advice for patients inhaling fenoterol at 80—120 litres/minute. We need more evidence of the benefit of advising a reduction of inspiratory flow rate to the level advocated by Newman et al. (1980), especially as there is doubt about the validity of extrapolating results to a different bronchodilator because of differences in particle size, propellant concentration and metered volume. Further investigation is needed to determine the best technique with which patients will comply.

Acknowledgements

We would like to thank W. B. Pharmaceuticals for supporting this work.

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A RETROSPECTIVE COMPARISON OF AMPICILLIN AND AMOXYCILLIN IN CHEST INFECTIONS

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Summary

Two hundred and fifty-five hospital in-patients with chronic bronchitis, bronchiectasis or pneumonia were treated with either ampicillin or amoxycillin. In a retrospective analysis no significant differences were found in survival or duration of hospital stay between the two regimes of antibiotic therapy.

Introduction

Ampicillin and amoxycillin have very similar activities but oral amoxycillin is better absorbed, less affected by the presence of food, and causes less diarrhoea (Neu 1979) and achieves a higher concentration in mucoid sputum (May & Ingold 1974). Various authors and the British National Formulary (1976) have therefore recommended amoxycillin instead of ampicillin (May & Ingold 1974; Neu 1979). In general medical wards in Hereford we observed a change from ampicillin to amoxycillin prescribing between 1975 and 1979 (Alexander & Wood 1981).

Despite persuasive pharmacological reasons for preferring amoxycillin, we have found only three double-blind comparisons studying respiratory tract infections (Anderson et al. 1979; MacKay 1980; Wright & Johnson 1980) none of which showed significant differences between the two drugs.

Hospital treatment should return patients to health and home as soon as possible, and a clinically superior antibacterial agent should improve survival and permit more rapid discharge. We have examined the records of the Hereford Hospital Prescribing Study (Barnett et al. 1978) to identify hospital patients who received ampicillin or amoxycillin and to compare survival and length of admission. Although retrospective, this study compares relatively large numbers of patients.

Methods

The Hereford Hospital Prescribing Study data permits retrospective analysis of the age and sex of patients, recorded diagnoses, duration of hospital stay, survival, and drug treatment. General medical in-patients admitted between 1975 and 1981 were selected who had primary diagnoses of acute or chronic bronchitis, bronchiectasis or pneumonia and who had been treated with ampicillin or amoxycillin. For comparison of the efficacy of the two drugs patients were excluded from the study for any of five reasons:

1. If both antibiotics were prescribed.

2. If the antibiotics were given by injection, with the exception of a single dose at the commencement of treatment, since only ampicillin was available for injection for most of the study.
3. If the antibiotic was started more than three days after admission.
4. If the antibiotic was given for less than three days.
5. If the patient was transferred to another hospital.

The ages and duration of stay of the remaining patients, the numbers of deaths, and the details of the duration and doses of ampicillin or amoxycillin were examined.

Table I. Comparison of patients treated with ampicillin or amoxycillin for lower respiratory tract infections

	Ampicillin		*Amoxycillin*	
Male	32		153	
Female	10		60	
Mean age ± SD (years)	67.5	(± 13.1)	67.2	(± 12.6)
Primary diagnoses:				
Bronchitis	21	(50%)	131	(62%)
Pneumonia	21	(50%)	81	(38%)
Bronchiectasis	—		1	
Died:	6	(14.3%)	24	(11.3%)
Mean duration of admission ± SD (days)	13.5	(± 15.5)	11.3	(± 9.9)
Discharged home:	36		189	
Mean duration of admission ± SD (days)	11.6	(± 5.9)	10.2	(± 8.2)
Mean duration of treatment ± SD (days)	7.4	(± 2.9)	7.0	(± 2.7)
Mean total dose ± SD (g)	12.3	(± 6.0)	7.4	(± 4.3)
Mean cost of drug treatment per patient (£)*	0.92		4.22	

* 1981 hospital purchase price.

Results

Two hundred and fifty-five patients were selected using the above criteria; 42 patients treated with ampicillin and 213 with amoxycillin. Characteristics of these patients are shown in Table I.

Both groups were of similar age but the ampicillin group had a death rate of 14.3% compared with 11.3% for the amoxycillin group. The distribution of primary diagnoses, the preponderance of men, and the durations of antibiotic treatment were very similar. The mean duration of admission of surviving ampicillin-treated patients was 11.6 days and of surviving amoxycillin-treated patients was 10.2 days. The differences in mortality and length of admission to hospital did not reach conventional levels of significance ($P < 0.05$).

Discussion

In this retrospective study we selected patients with common pulmonary infections who were treated with ampicillin or amoxycillin. Treatment with either was continued for about seven days. Although the ampicillin doses were larger, the cost of each course of amoxycillin was about four times greater than that of ampicillin. The hospital mortality and duration of stay were used to assess the efficacy of the treatment for 255 patients.

The mortality of ampicillin-treated patients was higher than that of amoxycillin-treated patients, but there were few deaths and the differences may have been due to chance. The mortality of ampicillin-treated patients was also slightly higher in the studies of Anderson et al. (1979) and MacKay (1980).

The length of stay in hospital, though a crude measure of the efficacy of treatment, is important for patients and has implications for cost. In our study, the surviving patients treated with ampicillin stayed in hospital for 11.6 days, compared with 10.2 days for patients treated with amoxycillin, but this difference was not statistically significant. The studies of Anderson et al. (1979) and Wright and Johnson (1980) showed little difference in duration of admission of patients treated with ampicillin and amoxycillin. None of these studies has been large enough to demonstrate a true advantage in favour of either drug.

The available evidence thus suggests that ampicillin and amoxycillin are of similar value in hospital patients with lower respiratory tract infections. If amoxycillin is no better than ampicillin, we have wasted about £700 of hospital resources by prescribing it to the patients reported here. Since ampicillin and amoxycillin together comprised 26% of all general practitioners' prescriptions for antibacterial agents in England in 1977 (Department of Health and Social Security 1978), and about 48% of hospital antibacterial prescriptions (Alexander & Wood 1981), it is astonishing that so few comparisons have been made. Although amoxycillin has largely replaced ampicillin in hospital use in medical wards in Hereford (Alexander & Wood 1981) this retrospective study has not shown any convincing benefit from the change.

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Does the Lung Work?

5. BREATHING IN AND BREATHING OUT

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Just over three hundred years ago, the Oxford physiologist John Mayow wrote:

> The lungs are placed in a recess so sacred and hidden that nature would seem to have specially withdrawn this part both from the eyes and from the intellect; for, beyond the wish, it has not as yet been granted to any one to fit a window to the breast and redeem from darkness the profounder secrets of nature. For, of all the parts of the body, the lungs alone, as if shrinking from observation, cease from their movement and collapse at once on the first entrance of light and self-revelation. Hence such an ignorance of Respiration and a sort of holy wonder. Still let me draw near to the inmost vitals, and concerning so obscure a matter, make at least a guess.
>
> In discussing on Respiration I shall follow the method pointed out by nature and begin therefore with inspiration . . .

Mayow had a very clear idea of the mechanics of breathing and was one of the first people to make a mechanical model of the lung. He put a bladder inside a pair of bellows that had a glass window on one side. He attached the bladder to the internal end of the pipe and observed it swell and empty as he made the bellows breathe in and breathe out. He was twenty-seven years old at the time.

In man, breathing in and breathing out are independent skills determined by separate factors and affected differently by various diseases. Like the breathing of alien gases discussed in a previous article, both abilities are easy to record but difficult to interpret. Recording is best done by obtaining a maximal flow–volume loop. The patient is normally asked to sit upright, legs uncrossed and back firm against the chair, and then told to inspire 'until they cannot get another drop in, attach themselves firmly to a mouthpiece, blow the insides out of the machine in front of them and, when they are completely empty, breathe it all back in again as fast and far as it will come'. After one or two practices, providing the instructions are vigorous and clear, most patients supply remarkably reproducible records of respired flow against respired volume (Fig. 1). It is often said that the inspiratory limb is less reproducible than the expiratory limb but our own experience is to the contrary (Fig. 2). The fact that curves of this complexity are highly reproducible means they are rich in information (whether or not that information can be understood at the time). In this article, we would like to discuss some of the things that can be said about curves of this sort.

The first observation, which can be made from Fig. 1, is that they are very similar from one normal subject to the next and surprisingly unaffected by posture. All of them, in essence, consist of a triangular expiratory limb (the upper part of the curve) with the apex of the triangle, representing peak expiratory flow, about 10% of the way along the expired volume axis. The inspiratory limb, by contrast, is smoothly curved, verging on the slightly rectangular, with its maximum depth near mid-inspiration. Peak expiratory flow is normally about two predicted forced vital capacities per second and peak inspiratory flow is usually slightly less, as shown in Fig. 3. As is well known, the forced expiratory volume in one second (FEV_1) is normally 65–80% along the expired volume axis, by which time expiratory flow has fallen to a quarter of its peak value, or less.

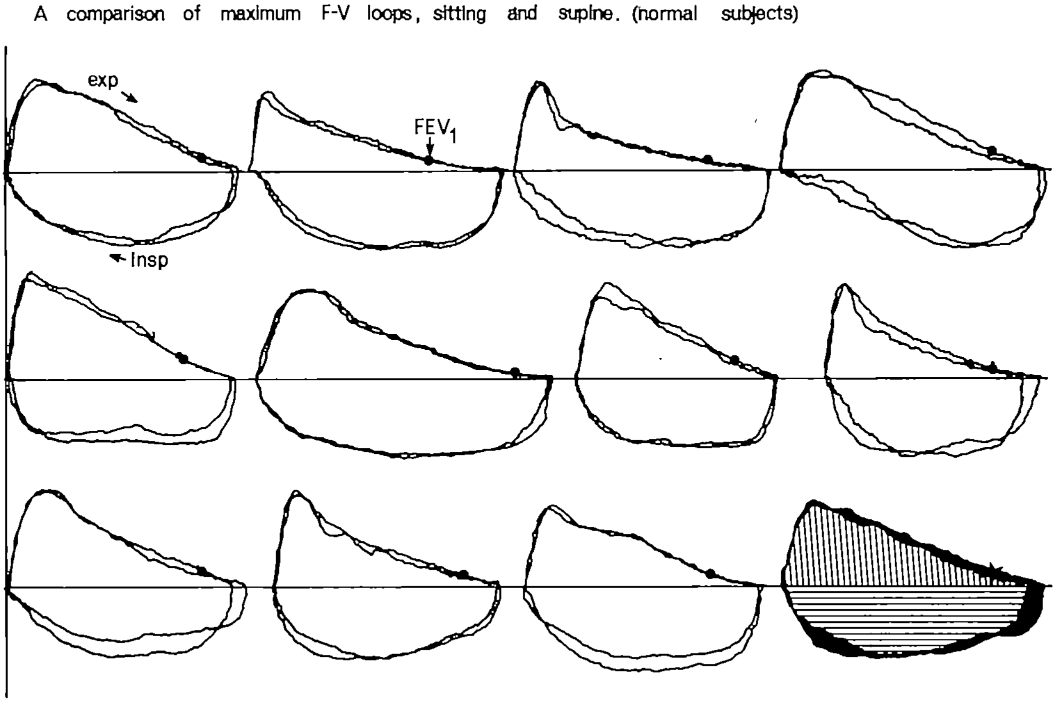


Fig. 1. Maximal flow–volume loops obtained from 12 normal subjects, once when sitting upright and once when lying down. The dots mark the points at which the FEV_1 was reached. We believe that best measure of the overall reproducibility of the loop is to compare half the area contained between loops by the maximum area contained by them (the solid and shaded areas of the bottom right loop, respectively)

The second observation, illustrated by Fig. 4, concerns the relation between the pressure applied to the lungs (by the chest wall) and the flow of air it produces at the lips. On inspiration these tally quite nicely, but on expiration they do not. That puts paid to any notion that the lung can be modelled by simply combining a compliant balloon and a rigid tube, because, as Mayow must have found out, all such models should expire more evenly and should empty completely as expiration proceeds.

Studies by Macklin, Hyatt, Mead, Macklem, Pride and many others, have established a much more credible model on which to hang our images of the lung.

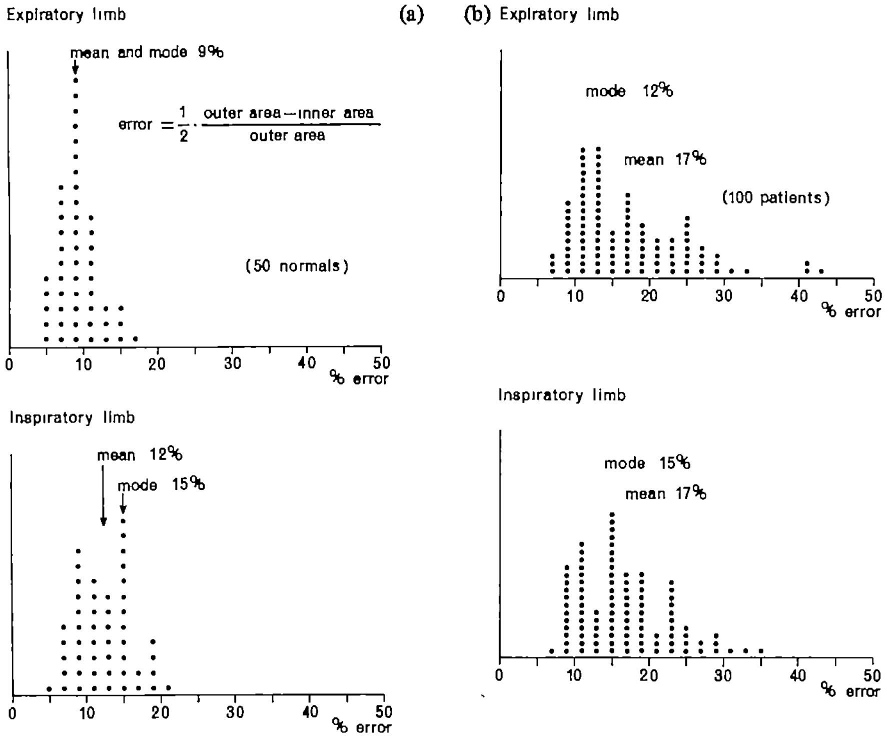


Fig. 2. Estimates of the reproducibility of the inspiratory and expiratory limbs, obtained as described in Fig. 1, in 50 normal subjects and 100 patients selected at random

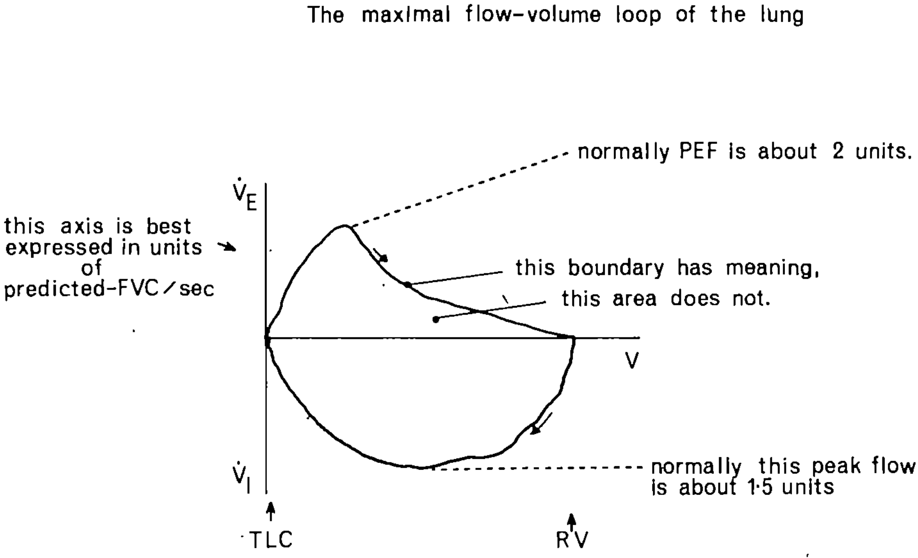
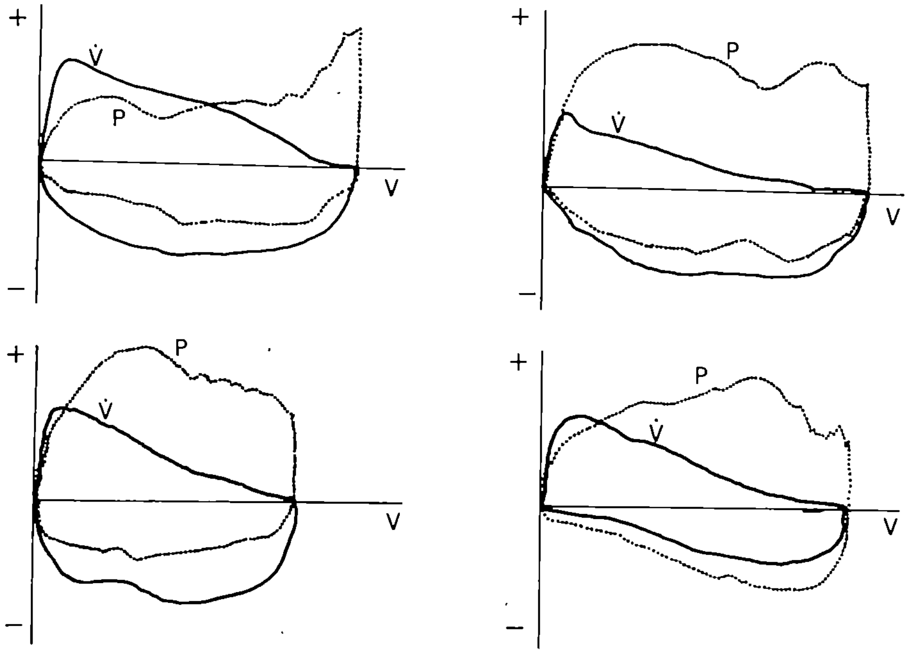

The maximal flow-volume loop of the lung
normally PEF is about 2 units.
V̇E
this axis is best expressed in units of predicted-FVC/sec
this boundary has meaning,
this area does not.
V
V̇I
normally this peak flow is about 1·5 units
TLC
RV

Fig. 3. Basic features of the flow–volume loop. The abbreviations V̇E, V̇1, TLC, RV, FVC and PEF stand for expiratory flow, inspiratory flow, respired volume, total lung capacity, residual volume, forced vital capacity and peak expiratory flow respectively

In this scheme, the airway is known to ramify to within a millimetre or two of every alveolus and must be extensile to allow the lung to expand. It is considered in three parts. The upper (extrathoracic) airway is surrounded by unsupported soft tissues and tends to cave in on inspiration and balloon out on expiration. The intermediate airway, which is intrathoracic but extrapulmonary in the sense that its walls are not directly attached to the lung, is exposed on its outer surface to pleural pressure and on its inner face to whatever happens to be endobronchial pressure at the time. Because it is not tethered to expanded lung this part is believed to be free to respond the moment that swings in pleural pressure are applied to its outer surface. That is to say, it tends to cave in as soon as expiration begins (pressure-dependent collapse) but balloons out as soon as breath is taken in. By contrast, the distal airway is intimately glued to surrounding lung tissue and is only free to collapse gradually as expiration proceeds (volume-dependent collapse).

A comparison of the forms of pressure and flow loops during maximal manoeuvres



(four 'normal' males aged 27, 32 33 and 47 years)

Fig. 4. Simultaneous flow (V̇) and oesophageal (i.e. pleural pressure (P)) traces obtained during maximal flow–volume loop manoeuvres in four healthy men

As John Mayow observed, the lungs 'collapse at once' when the chest is opened, and shrink tô a small volume because of their natural recoil pressure. It is greatest when the lungs are full. This passive elastic pressure, which aids breathing out and opposes breathing in, reflects the stiffness of the lung. It helps us interpret the maximal flow–volume loops described earlier. Fig. 5a shows one such curve, obtained from a normal subject. Fig. 5b depicts the pleural (i.e. oesophageal) pressure swings that produced it. At the start of the manoeuvre the lungs were held open by a negative pleural pressure of -30 cm H_2O, which was just sufficient to keep them full. On forced expiration pleural pressure rose and remained at 40 cm H_2O or more until residual volume was achieved, although the flow fell progressively, reaching zero when the applied pressure was 60 cm H_2O. The fact that air flow falls to zero at residual volume, when the lung is known to contain one to two litres of gas and has a high positive pressure applied to it, implies that at some point in their course all paths from the alveoli to the mouth must be shut off completely.

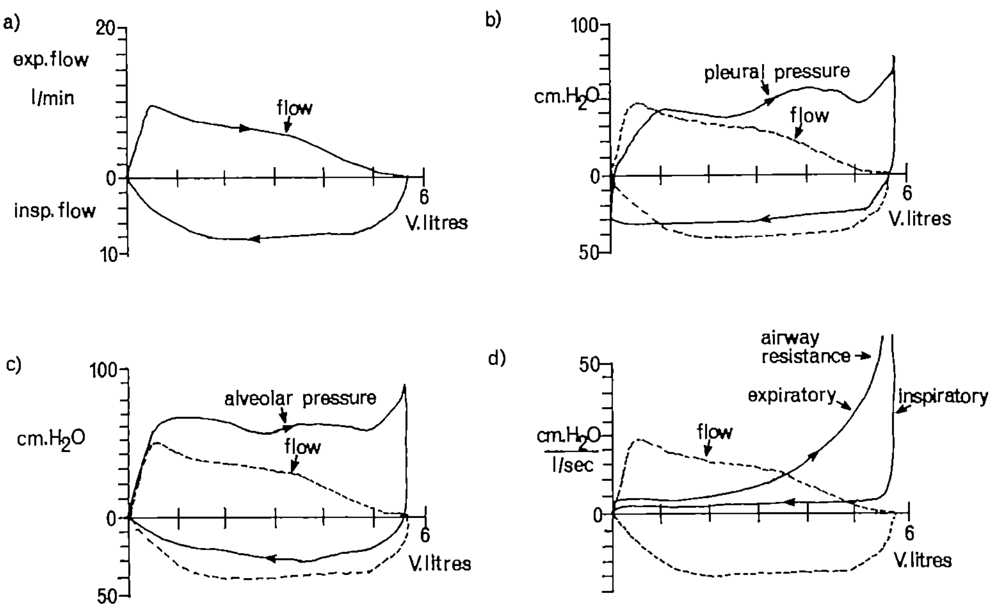
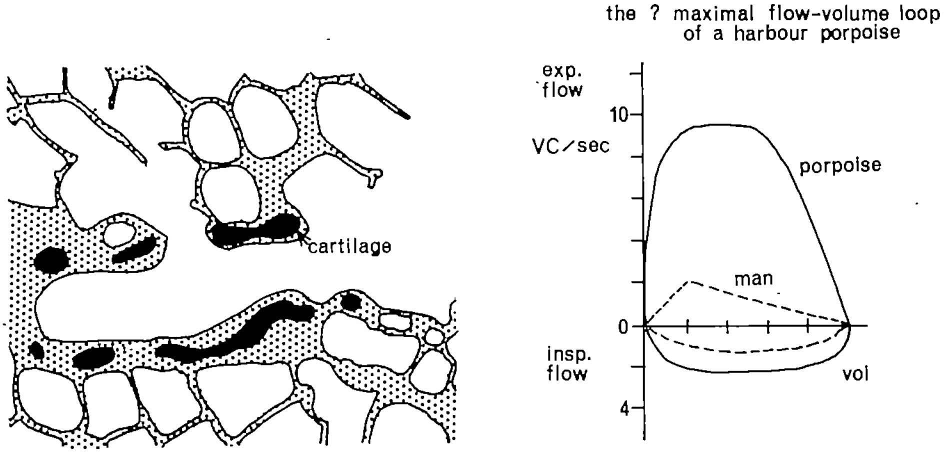

The mechanics of breathing out and breathing in.

Fig. 5. (a) Flow–volume loop obtained from a normal subject. (b) The oesophageal pressure trace obtained at the same time. (c) The alveolar pressure trace derived by combining the oesophageal trace with this static pressure–volume curve. (d) The airway resistance computed from alveolar pressure and flow at the mouth

Throughout the manoeuvre the driving pressure (i.e. alveolar pressure) forcing gas through the airway, is the sum of pleural and elastic recoil pressures at each stage of lung volume. This pressure is shown in Fig. 5c. It exceeds pleural pressure by $+30$ cm H_2O at TLC and by a few cm H_2O at residual volume. Overall airway resistance, which is obtained from Fig. 5c on dividing alveolar pressure by air flow, is shown in Fig. 5d. On expiration it rises slowly to begin with and then much faster, as the lungs shrink, but on inspiration it immediately drops to a low level that falls slightly further still as the lungs re-expand.

The sites of increasing airway resistance during forced expiration and of airway closure at residual volume differ from one patient to the next and probably vary in normal people as well. In principle, as others have described, it is believed that some floppy segments in the airway collapse part way through expiration, behaving either as a Starling resistor (i.e. a very floppy element) or an aerodynamic choke point, across which the major pressure-drop within the airway occurs. These segments may well lie in the medium-sized branches of the bronchial tree and recede distally as expiration proceeds.

The benifits of re-inforcing small airways



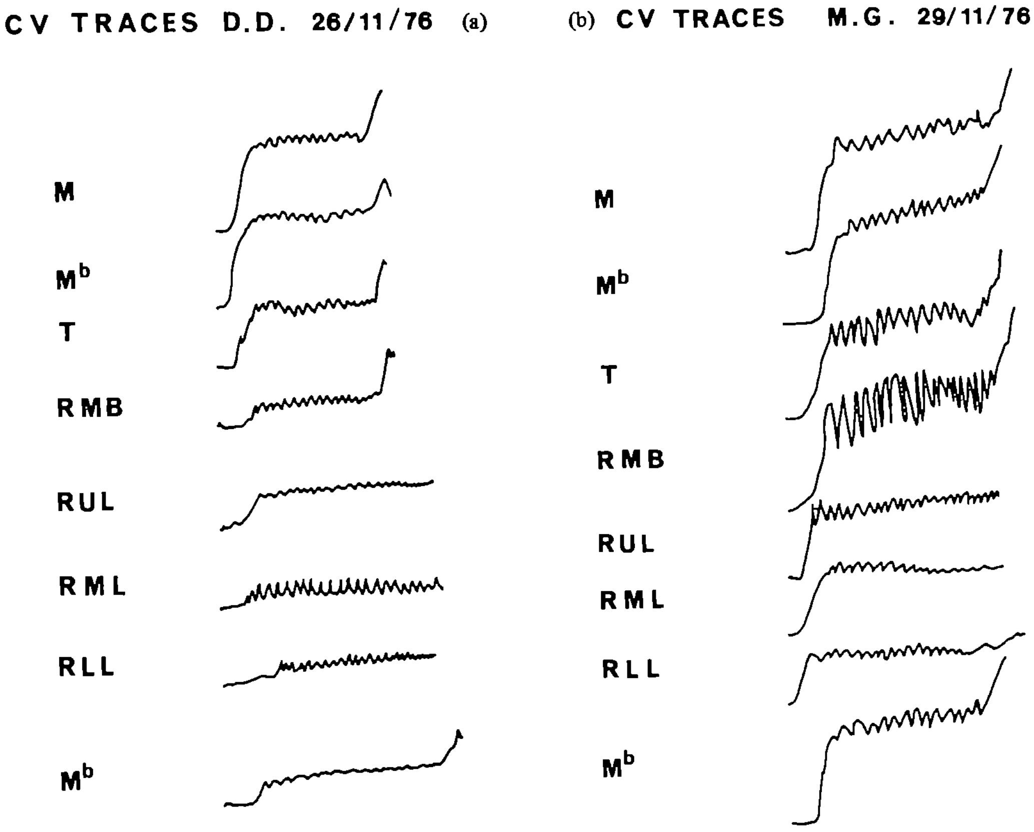
the ? maximal flow-volume loop of a harbour porpoise

(drawn from section of sea-lion lung)

(data of Kooyman & Cornell, 1981)

Fig. 6. (a) Typical distribution of cartilage in a terminal airway of a sea-lion lung. (b) Comparison of the maximal flow volume loops of a man and a Harbour porpoise. Vital capacity is on the abscissa and flow in VC/per minute is on the ordinate

Some comparative studies support the idea that the flow-limiting segments lie in the distal airways. Unlike their terrestrial counterparts, all marine mammals have airways that are reinforced with muscle and or cartilage all the way to the alveoli. As was mentioned previously in this series, the prime result of this adaptation is protection from the chemical hazards of diving. When the animal dives, its chest wall is compressed, driving gas out of the alveoli into the more rigid airways, away from pulmonary capillary blood. However, making the small airways some five times stiffer than the alveoli is sufficient for this purpose, but sea-lions and dolphins have much more reinforcement than that. It apparently allows them to breathe very rapidly during brief visits to the surface, by endowing their maximal flow–volume loops with expiratory limbs that are steep and tall. This is especially obvious when the whole loop is scaled in FVC/sec and compared with that of man (Fig. 6). By contrast, direct inspection and closing volume studies, during bronchoscopy in man, suggest *lobar* and *segmental* bronchi may close off completely towards the end of maximal forced expiration (Fig. 7). Such closures do not exclude shut-down at other more distal points along the airway during the same manoeuvre.


CV TRACES D.D. 26/11/76 (a)

(b) CV TRACES M.G. 29/11/76

Fig. 7. Traces of respired helium concentration recorded in two subjects at the mouth before bronchoscopy (M) and after passage of the fibrescope (Mb), and in the trachea (T), right main bronchi (RMB), right upper, middle and lower lobal bronchi, and at the mouth again, during closing volume manoeuvres. Each expiration was preceded by inhalation of a 300 ml bolus of helium at the onset of inspiration. In both subjects the closing volume artefacts seen in the trachea and RMB were not seen in the lobes, and so were presumably generated by closure of the RMB. This was seen on direct inspection, in both cases, as residual volume was approached

When people make forced expirations from submaximal volumes they are confined by the same performance envelope as if they had begun at TLC (Fig. 8). This is true even in coughing and emphasizes that this is a true limit to the expiratory capability of the lung. However, the moment the forced expiration begins the pressure-sensitive elements of the intrathoracic airway collapse, expelling a small additional pulse of air, which is due to the dynamic compression but is not a true expiratory flow at all. It is more obvious in emphysematous than healthy lungs because the volume of pressure-dependent collapse is great and the true expiratory flow is often very small.

When healthy lungs perform forced expirations from submaximal volumes the 'FEV_1/FVC' ratio of the artificially constrained lung falls with the apparent TLC, as shown in the right-hand part of Fig. 8. This indicates that as the lung empties, airway resistance rises more quickly than the 'vital capacity' falls. This is quite contrary to the behaviour of diseased lungs (see later) and has to be kept in mind when interpreting even the simplest spirometry in patients.

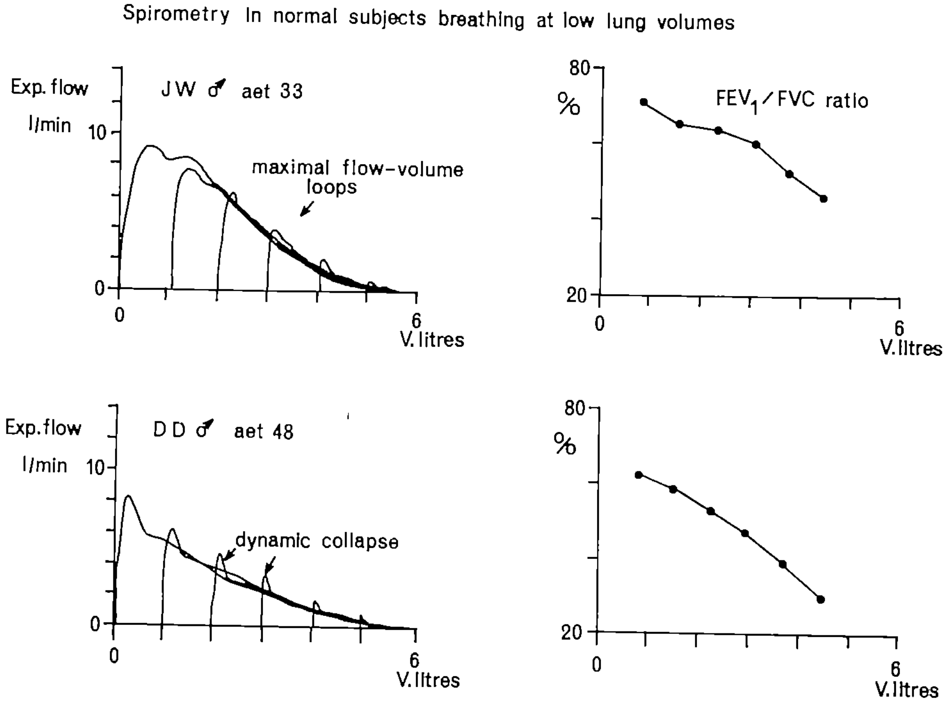


Fig. 8. The expiratory flow–volume loops and computed FEV_1/FVC ratios seen when two normal subjects made maximal manoeuvres beginning at 0, 1, 2, 3, 4 and 5 litres below TLC

As common sense suggests, when people breathe through an artificial resistance to expiration their loops show a distorted expiratory limb but a normal curve on breathing in (Fig. 9a). When they breath through an inspiratory resistance the reverse is true (Fig. 9b) and when the obstruction is common to both phases both limbs are affected (Fig. 9c). The expiratory limb always shows an inflection where the limiting effect of the added resistance is overtaken by that of the shrinking airway (Fig. 9d).

These simple observations are very helpful when looking at the loops that are generated in disease. The effect of an obstruction occurring in a main airway will depend upon its site (extra- or intrathoracic), the stiffness of local and remote parts of the airway wall, and whether there is any pulmonary disease that modified

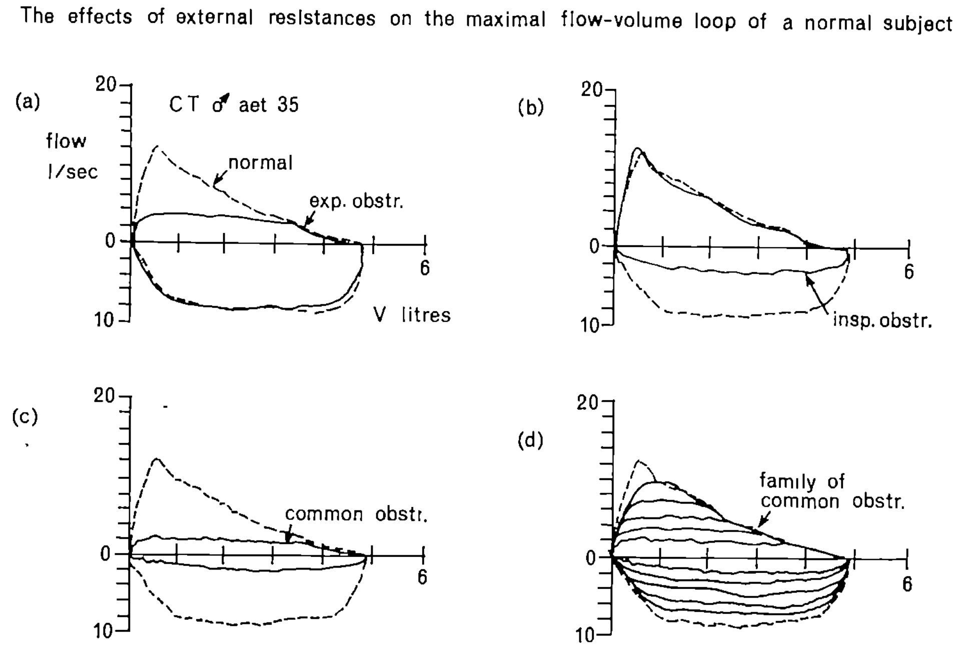


Fig. 9. Flow–volume loops recorded in one normal subject breathing through external resistances. Note the inflection points where the obstructed expiratory curve meets the normal curve

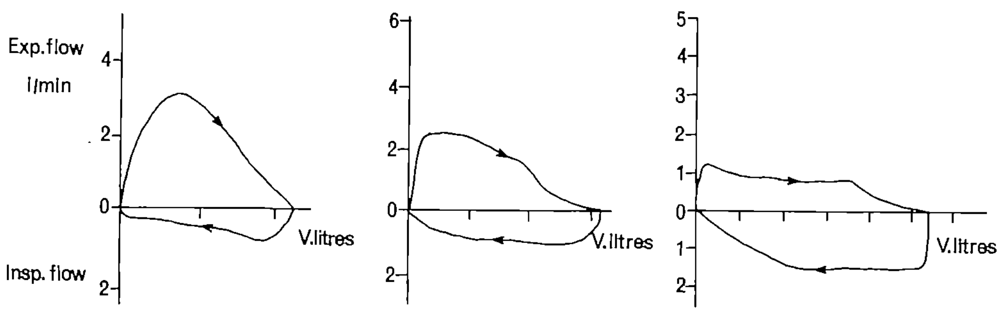
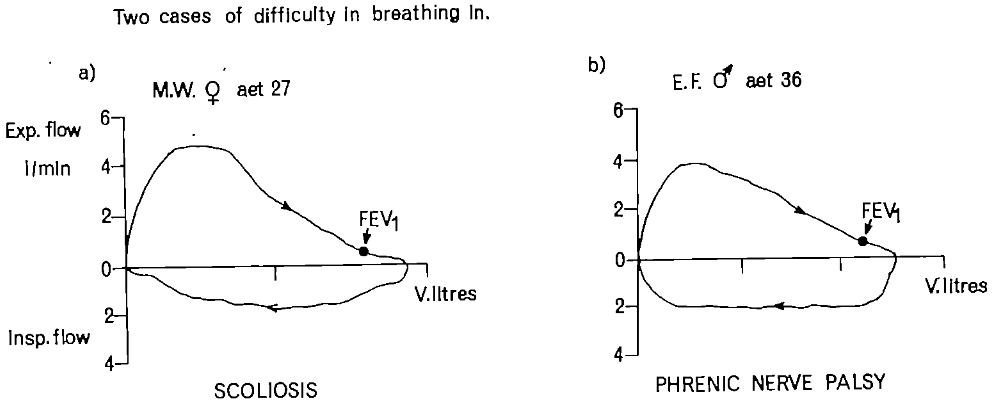


Fig. 10. Three types of main airway obstruction. (a) Non-rigid extrathoracic obstruction in a young woman with bilateral vocal cord palsies. (b) Rigid extrathoracic obstruction in a middle-aged woman with tracheal compression from a carcinoma of the thyroid. (c) Rigid intrathoracic obstruction in a middle-aged man with a carcinoma of the trachea 3 cm proximal to the main carina

the shape of the loop before. If there is a flaccid segment in the extrathoracic airway, as seen in bilateral vocal cord palsy or tracheomalacia, the increased resistance to airflow will only be present during inspiration. The loop then shows a normal expiratory limb but very low flows on breathing in (Fig. 10a). A rigid extrathroacic tracheal obstruction will oppose both phases of breathing but will be more obvious on breathing in than out because the extrathoracic element below the rigid obstruction will tend to cave in more markedly than before (Fig. 10b). An identical lesion occurring within the chest has diametrically opposite effects, in that it truncates both limbs of the loop but affects the expiratory limb more markedly since the intrathoracic element above the rigid obstruction will cave in more than before. The inflection point at which general exceeds local resistance is very obvious on such expiratory curves (Fig. 10c). However, it must be borne in mind when interpreting the flow–volume loop in upper airway


Two cases of difficulty in breathing in.

SCOLIOSIS

PHRENIC NERVE PALSY

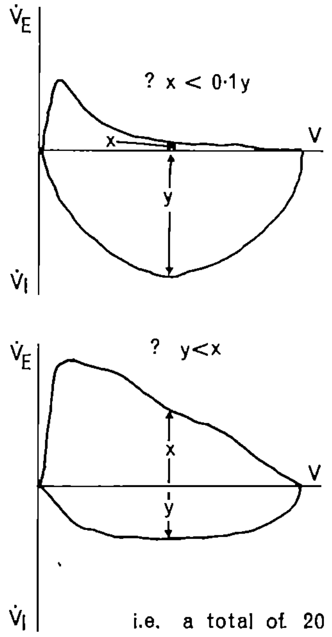
Fig. 11. The maximal flow-volume loops seen in a 27-year-old lady with scoliosis and a 36-year-old man with phrenic palsy

obstruction that these basic patterns will only be seen in the presence of relatively normal intrapulmonary airways. When the latter are significantly diseased, the additional effects of increased extrapulmonary resistance to either breathing in or breathing out may be masked.

Although airway resistance is a major determinant of both limbs of the flow–volume loop, other factors are also important, for example the strength of the diaphragm and the rigidity of the chest wall. Fig. 11 shows the flow–volume loops from two such patients. The first is from a lady aged 27. Its inspiratory limb is clearly very flattened but her inspiratory airway resistance was normal (i.e. < 0.2 kPa/litre/sec), her lungs were rather small (55% of predicted TLC) and her FEV_1/FVC ratio was *high* (90%). She had scoliosis. The second loop, which is very similar, comes from a man aged 36. He also had small lungs, normal airway resistance and a high FEV_1/FVC ratio. In addition he had a high *K*CO, which often indicates that the lung has a normal capillary blood volume but is prevented from expanding by some extrapulmonary cause. He was known to have a right recurrent laryngeal-nerve palsy but this does not limit expansion of the lung or raise *K*CO. The combination of loop, TLC and *K*CO findings prompted a search that revealed an unsuspected phrenic palsy.

In our laboratories at least, upper airway obstruction, phrenic palsy and chest-wall deformity are important but uncommon causes of inspiratory airflow limitation. Much the commonest is stiffening of the lung. To illustrate this point in more detail, we have taken a random sample of 3000 flow–volume loops from a library of more than 10 000, and have identified all those that met one of two criteria: either that the expiratory limb was so flattened that mid-expiratory flow was less than 10% of mid-inspiratory flow; or that the inspiratory limb was so reduced that mid-inspiratory flow was less than that in mid-expiration (Fig. 12). As the figure shows, the first type of loop, which is typical of emphysema, was not seen in any normal subjects. The second pattern, with the suspiciously flat inspiratory limb, was seen in only 6.8% of healthy people (mainly children and young women) but was found in 11.5% of the patients coming to the laboratory, most of whom were neither children or young women. The 572 people isolated for this study had a full set of routine lung function tests, i.e. spirometry before and after bronchodilator, whole-body plethysmography and single breath carbon-monoxide transfer characteristics.

In 3000 loops randomly drawn from > 10,000 :



this shape, which is not seen in any normals, was found in 8·5% of patients

this shape, which is seen in only 6·8% of healthy people (mainly children and young women), was found in 11·5% of the patients.

i.e. a total of 20 % of loops met the criteria.

Fig. 12. Details of the 'emphysematous' and 'fibrotic' loop shapes that were selected for further study

The first finding from this simple study is that the 'emphysematous' loops are typically *but not always* associated with an increased TLC (Fig. 13a). Eleven of the 248 patients had lungs smaller than 85% of predicted TLC. Such patients are obviously worth investigating further, for chondromalacia or co-existing

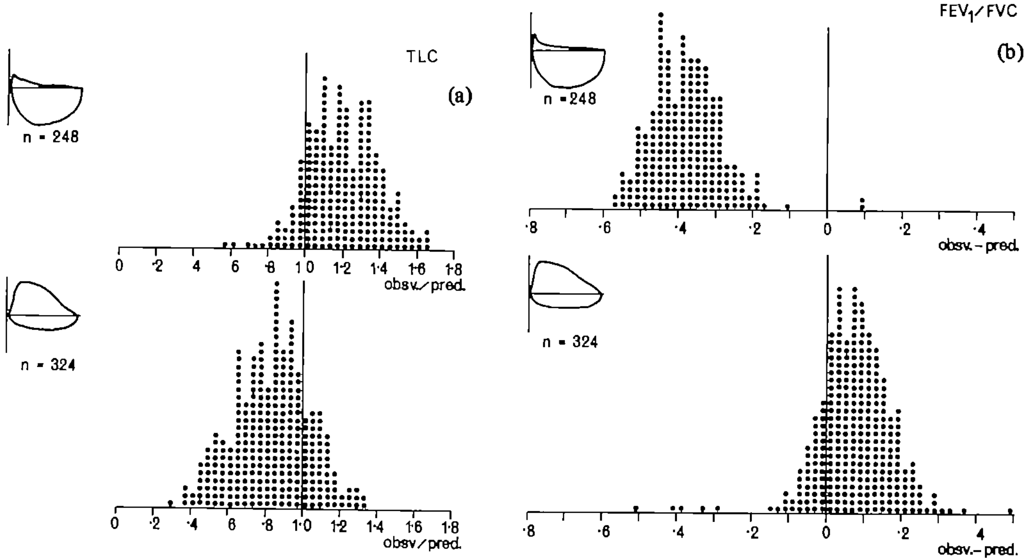


Fig. 13. Frequency histograms of the total lung capacities (TLC), expressed as observed divided by predicted values, and the FEV_1/FVC ratio, expressed as observed minus predicted values, associated with the two loop shapes under study

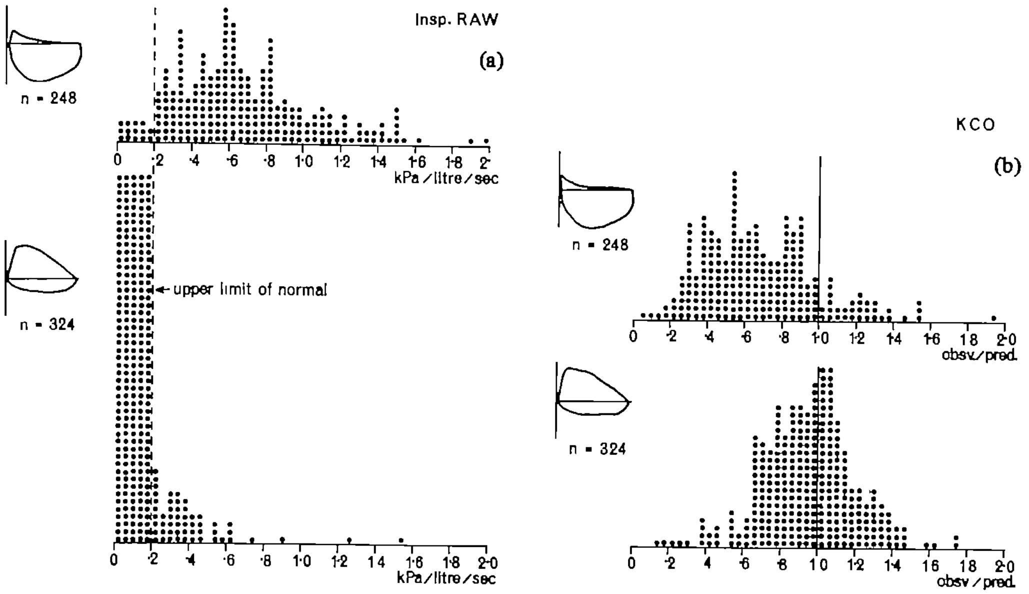


Fig. 14. Frequency histograms of the inspiratory airway resistance (expressed in kPa/litre/sec) and carbon monoxide transfer per litre of accessible gas volume (*K*CO), expressed as observed divided by predicted values, associated with the two loop shapes under study

restrictive lesions. The other group of loops, which we instinctively associate with fibrosis, were typically, *but not always,* associated with small lungs. Fifteen of the 324 patients had lungs that exceeded 115% of predicted TLC. Such people are especially worth investigating for extrathoracic obstruction.

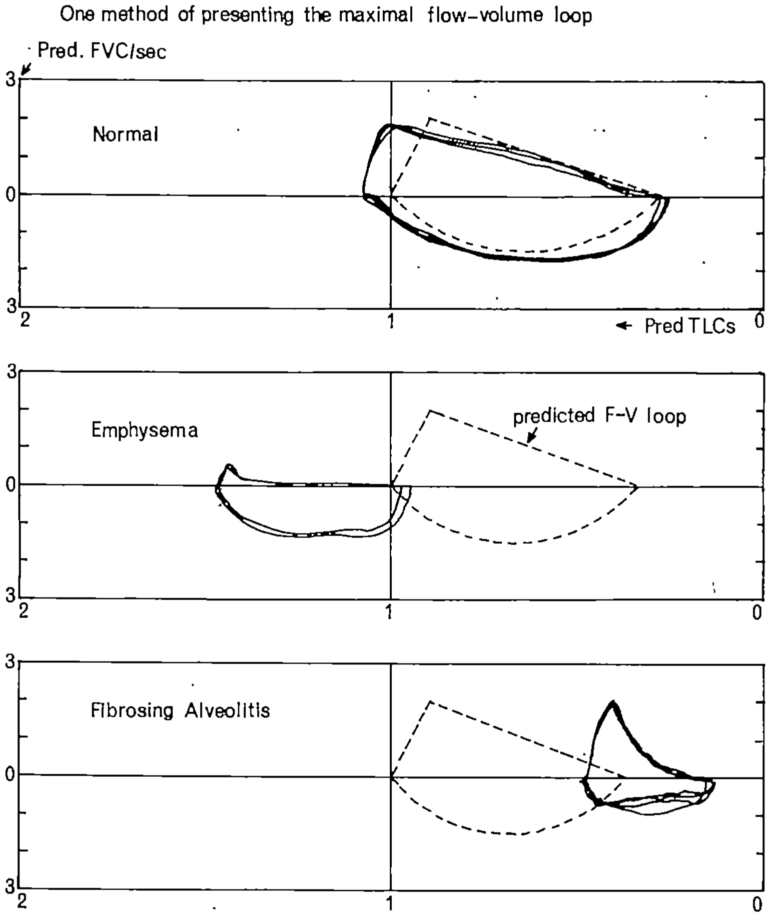


Fig. 15. A method of presenting flow–volume loops when absolute lung volume is known. The vertical boundaries of each box mark respired flow, scaled in predicted FVC/sec. The horizontal boundaries are scaled in predicted FVC/TLC. Records are from a healthy man aged 48, a 57-year-old man with emphysema and a 62-year-old man with fibrosing alveolitis. Note the scooped-out expiratory limb on the latter's curve, which indicates that he also had an obstructive defect

The next point to be made concerns the ratio of FEV_1 to FVC. Unlike the lungs of healthy people the large lungs of the 'emphysematous' group had low ratios and the small lungs of the 'fibrotic' group had high ratios (Fig. 13b), emphasizing the role of elastic recoil pressure in expelling the FVC. For reasons that are not altogether clear, it is customary in our own as in most laboratories, to measure airway resistance in inspiration, when it is least likely to be detected.

Knowing that emphysematous lungs have a low recoil pressure and that much the same oesophageal pressures are generated on inspiration and expiration, it is obvious that the 'emphysematous' patients must have airway resistances on expiration that are at least ten times higher than the already high ones recorded when they first breathe in (Fig. 14a). By contrast, inspiratory obstruction is a rare accompaniment of inspiratory airflow limitation, seen in 15% of the 324 patients studied here. We normally take that combination of a flat inspiratory limb and a raised resistance at the start of breathing in, as an indication for upper airway investigation, (usually bronchoscopy). As mentioned earlier, *K*CO can be regarded as a measure of the accessible pulmonary capillary blood volume. We expect it to be low in 'emphysematous' and 'fibrotic' conditions but this is not always so (Fig. 14b). High values imply that the accessible part of the lung is over-rich in haemoglobin, either because of diversion, an extrapulmonary limit to expansion or bleeding. Such cases (Fig. 14b) frequently repay further study.

Finally, if practical, it is often helpful to view the maximal flow–volume loop in combination with TLC. This can be done quite easily, by scaling the ordinate and abscissa in terms of predicted FVC/sec and predicted TLC, as shown in Fig. 15. We find this gives a more vivid impression of the difficulties individual patients experience in breathing in and breathing out.

Suggestions for Further Reading

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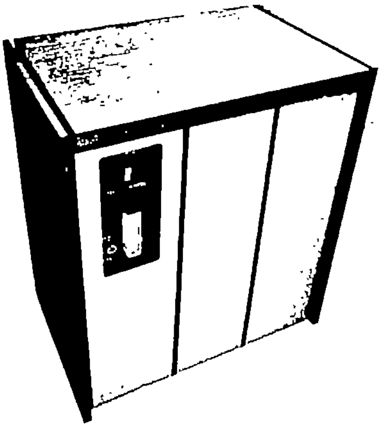

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LATE ENDOBRONCHIAL METASTASIS FROM OVARIAN TUMOUR

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Symptomatic endobronchial metastases are uncommon (Braman & Whitcomb 1975), usually arising from primary tumours in kidney, breast or colon or from malignant melanoma. We found only two case reports (Freedlander & Greenfield 1942) of such metastases from ovarian malignancies and we report a further such case.

Case Report

A 45-year-old housewife presented in 1968 with a history of amenorrhoea and dragging abdominal pain. At laparotomy a stage IIb bilateral ovarian serous cystadenocarcinoma of borderline malignancy was found with numerous secondary deposits in the pouch of Douglas. Bilateral salpingo-oophorectomy and hysterectomy was carried out and 15 mg of thiopeta was instilled into the pelvic cavity. Following operation a course of pelvic irradiation was given and an additional 225 mg of thiopeta was administered intravenously.

The patient remained well and regular follow-up showed no evidence of recurrence until March 1980 when a dense right mid-zone shadow was seen on her chest radiograph. In October the patient developed a persistent dry cough with stridor and a further chest radiograph showed that the opacity had doubled in diameter. Computerized tomographic scanning of the thorax, abdomen and pelvis demonstrated no firm evidence of other metastatic spread. At bronchoscopy a smooth, rounded mucosa-covered tumour was seen protruding from the apical segmental bronchus of the right lower lobe. This proved to be secondary ovarian serous cystadenocarcinoma containing numerous psammoma bodies. At right thoracotomy numerous very small subpleural secondary deposits were revealed and a right lower lobectomy was performed to reduce the tumour mass.

DISCUSSION

Some 30% of extrathoracic malignancies show evidence of pulmonary metastases at autopsy. Macroscopic endobronchial secondaries in the large airways occur in only 2%, though the microscopic incidence may be as high as 25–50% (Baumgartner & Mark 1980). The most common primary sources are kidney, breast, colon and malignant melanoma and we could find only two cases in the literature of endobronchial secondaries from a primary ovarian growth. Ovarian cystadenocarcinoma and cystadenoma of borderline malignancy spread locally and both haematogenous spread and extension outside the abdominopelvic cavity are rare (Hart 1977). Late recurrences of the borderline malignant type are well recognized, but they are almost always local and the histology remains unchanged.

The symptoms and signs of endobronchial secondary deposits may mimic those of primary bronchogenic tumours and a long time interval between diagnosis of the primary and presentation of the secondary is not infrequent, Baumgartner and Mark (1980) reporting a median period of five years (range six months to 12 years). In our case the interval was 12 years and we thought initially that the lesion was a primary bronchogenic malignancy.

In conclusion, endobronchial lesions may, in people with a previous history of malignancy elsewhere, be secondary deposits even when the latent period is long and even when the previous malignancy is one rarely associated with such deposits. Differentiation from a primary bronchogenic lesion (benign or malignant) is important therapeutically and prognostically.

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A PILOT STUDY OF 'AUGMENTIN' IN LOWER RESPIRATORY TRACT INFECTIONS: PHARMACOKINETIC AND CLINICAL RESULTS

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Summary

Thirteen patients with a mean age of 67 years admitted to hospital with signs and symptoms of lower respiratory infections were treated with 'Augmentin' (500 mg amoxycillin + 250 mg clavulanic acid) given orally every 8 hours, for 7 days. The clinical response was 'good' in ten cases and one 'failed'. Two patients could not be assessed. Side-effects were not serious: only one patient had to stop treatment (due to diarrhoea). The pharmacokinetic results show that peak levels of amoxycillin and of clavulanic acid in the blood and in sputum are achieved at a later time in the patients studied than occurs in healthy volunteers.

Introduction

Clavulanic acid is a naturally-occurring inhibitor of β-lactamase (Reading & Cole 1977), which when combined with amoxycillin (as 'Augmentin') results in a broad-spectrum combination, active against strains such as ampicillin-resistant *Escherichia coli, Klebsiella aerogenes* and *Staphylococcus aureus.* 'Augmentin' has already shown considerable promise in the treatment of urinary infections, especially those caused by resistant organisms (Ball et al. 1980; Kosmidis et al. 1980; Leigh et al. 1981). In the present study we have investigated the use of 'Augmentin' in patients admitted to hospital because of severe lower respiratory tract infections. We have also determined the concentrations of amoxycillin and clavulanate obtained in the sputum, saliva and blood at various times during treatment in these patients.

Patients and Methods

Thirteen patients entered the trial; they presented at the Royal Northern Hospital with signs and symptoms of acute lower respiratory tract infections serious enough to warrant admission into hospital. Ten had exacerbations of chronic bronchitis, two had pneumonia and one a lung abscess. Nine were male, four female; their ages ranged from 26 to 88 years, with a mean of 67.2. All but four of the patients had at least one other underlying medical condition, most often congestive heart failure. In three patients the serum levels of creatinine were abnormally high immediately before being admitted. All had received an appropriate course of an oral antibiotic to which the response had been unfavourable.

Treatment regimen

Each 'Augmentin' tablet contains a combination of 250 mg amoxycillin as the trihydrate and potassium clavulanate equivalent to 125 mg of the free acid (Beecham Research Laboratories Ltd). Patients received two of these tablets by mouth every 8 hours for 7 days.

Therapeutic assessment

The results of treatment with 'Augmentin' were assessed by the clinician in charge of the patient. The response was 'good' if the patient was restored to his previous state of health; if no improvement occurred, the treatment was judged to have 'failed'.

Specimen collection and processing

Sputum was collected for microbiological examination immediately before treatment and again on day 8. Sputum, saliva and plasma were collected one hour after a dose on the second and seventh day for measurement of drug levels.

Microbiological procedures

Sputum specimens were weighed and then homogenized using the Colworth 'Stomacher' (A. J. Seward, Bury St Edmunds). If necessary a small measured amount of sterile saline was added and a correction made for the dilution. White cells in the homogenate were counted using a counting chamber, and the number of bacteria present estimated by plating out 0.1 ml volumes on the following media: two plates of Columbia agar (an enriched agar for growing fastidious organisms) containing 7% whole horse blood, one MacConkey agar, one chocolate agar. One of the blood agar plates was incubated anaerobically (using the GasPak system), and the remainder were incubated aerobically. Plates were inspected after overnight incubation. Gram-positive cocci and *Haemophilus influenzae* were identified according to Cowan (1974), and coliforms by the API 20E system. Sensitivity testing was carried out by the disc method on Isosensitest agar (Oxoid), with the addition of lysed or heated blood as appropriate.

Assay techniques

Sputum specimens were homogenized as described above. Plasma was separated from the blood samples by centrifugation. Saliva specimens were assayed without further processing. All assays were carried out on the same day that the specimens were taken. Each component of 'Augmentin' was determined by an independent microbiological assay, using *Sarcina lutea* NCTC 8340 as the indicator organism for amoxycillin and *K. aerogenes* NCTC 11228 for clavulanate. The assay system was based on that described by Brown et al. (1976).

Patients' plasma were diluted 1:5, 1:10 and 1:25 in pooled plasma and each dilution was plated in triplicate. Sputum and saliva specimens were plated undiluted in triplicate.

Results

'Augmentin' was given to 13 patients; of these, 11 received 7 days' treatment and were thus assessable for clinical efficacy under the terms of the protocol. The other two patients were not assessable. However, we used results from all the patients for the assessment of side-effects and in the pharmacokinetic analysis.

Microbiological results

The pathogens isolated from the patients entered into the study are shown in Table I. Two patients (nos. 3 and 13) were infected with two pathogens, six had a single pathogen, and we were unable to isolate a pathogen in four. Patient 5 could not produce any sputum. The isolation rate was thus eight out of 12 (67%). Of the 11 clinically assessable patients (nos. 2, 3, 4, 5, 6, 7, 8, 10, 11, 12, 13) five had pathogens in the first sputum specimen (see Table I): in four of the latter group, the original pathogen was absent following the course of 'Augmentin'. In the fifth patient (patient 8 in Table I) the pathogen (*E. coli*) persisted, but in reduced numbers (10^5/ml – compared with the original count of > 10^7/ml) in sputum taken on the day after the end of treatment.

In six patients the sputum purulence, assessed by quantitative white cell counts in homogenized specimens, dropped markedly during the course of treatment (from a mean value of 14 000/mm^3 to 420/mm^3). In the three other patients from whom two separate specimens were obtained at 7-day intervals sputum purulence was virtually unchanged; in two of these, no pathogen had been isolated initially.

Table I. Respiratory pathogens isolated from patients treated with 'Augmentin'

Bacterial species	*Patient no.*	*Sensitivity*	
		Amoxycillin	*'Augmentin'*
Streptococcus pneumoniae	13	S	S
Streptococcus, gp C	3	S	S
Streptococcus, gp G	7	S	S
Escherichia coli	1*	R	S
	8	S	S
	11	S	S
Klebsiella aerogenes	9*	R	S
	12	S	S
Haemophilus influenzae	3	S	S
	13	S	S
No pathogen isolated	2, 4, 6, 10		

* These two patients were not clinically assessable.

Clinical results and side-effects

Of the 13 patients who entered the trial, the clinical results were 'good' in ten, 'failed' in one and 'not assessable' in two. The patient that failed died despite having completed the course of 'Augmentin': an autopsy showed left lower lobe pneumonia and chronic bronchitis. Attempts to isolate the original infecting organism (*K. aerogenes*) were unsuccessful. One of the 'not assessable' patients did not complete the 7-day course (see 'Side-effects' section), while the other had faked his fever. It was decided not to classify the latter patient as a 'failure': indeed, the fact that he had decided to tamper with his sputum and falsify his temperature suggested that he had improved under treatment with 'Augmentin'.

Treatment was stopped in only one patient (suffering from cryptogenic cirrhosis) who developed moderate diarrhoea, but no pathogen was isolated from the faeces.

Pharmacokinetic results

The concentrations of amoxycillin and clavulanate found in plasma, sputum and saliva specimens are shown in Table II. Concentrations of amoxycillin measured on day 6 were not significantly different from those found on day 2; this also applied to levels of clavulanate. Hence, we felt it justifiable to calculate mean values for the combined data obtained on days 2 and 6. It is clear from a consideration of the size of the standard deviations that there was a wide scatter of drug concentrations.

Table II. Concentrations of amoxycillin and clavulanate in specimens of plasma, sputum and saliva taken 1 hour after patients had swallowed two tablets of 'Augmentin' (500 mg amoxycillin + 250 mg clavulanate), on the second and seventh days of the course of treatment

Antibiotic	*Concentration* (μg/ml) (mean values ± SD, with no. of specimens in parentheses)		
	Plasma	*Sputum*	*Saliva*
Amoxycillin	3.87 ± 3.65 (22)	0.26 ± 0.28 (17)	0.12 ± 0.18 (19)
Clavulanate	2.59 ± 2.5 (22)	0.23 ± 0.14 (7)	0.44 ± 0.41 (7)

Results were not significantly different on the two days (see text) and overall mean values are given.

Discussion

The plasma levels of amoxycillin we observed during the present study were markedly lower than those reported by other workers. For instance, Sutherland et al. (1972), Steward et al. (1974) and Ingold (1975) found peak levels of 10.8, 11 and 7.6 μg/ml. We can suggest three reasons which may explain our results. First, specimens were collected (as dictated by the protocol) 1 hour after giving the drug, while peak levels of amoxycillin do not occur until 2 hours in healthy volunteers (Sutherland et al. 1972). Second, in elderly patients such as those studied by us (many of whom had chronic cardiac failure), it is known that absorption of orally administered drugs may be delayed. For ampicillin mean values of times for peak concentration were 2.08 hours in young subjects but 3.09 hours in elderly patients (Triggs et al. 1980). Third, subjects confined to bed show lower peak levels of amoxycillin than do ambulant subjects (Roberts & Denton 1980). Thus in future studies of this type blood samples should be taken 3 hours after the dose of 'Augmentin'.

Sputum levels of amoxycillin observed are very similar to those found in other patients with chronic respiratory conditions (May & Ingold 1972; Ingold 1975).

Sputum concentrations were as high on the penultimate day of treatment, when purulence had decreased, as on the first day. In this respect we agree with the findings of May and Ingold (1972).

Levels of amoxycillin in both the plasma and sputum were not significantly higher than those of clavulanate ($P > 0.05$) despite the fact that the dose of amoxycillin was twice that of clavulanic acid. However, in the saliva significantly higher concentrations of clavulanate than amoxycillin were found ($P < 0.05$).

Plasma levels of clavulanate were a little lower than those reported by Munch et al. (1980) and Hoffler and Dalhoff (1980), and the same arguments might apply to this compound as to amoxycillin with regard to reasons for delay in reaching peak levels.

Sputum concentrations of amoxycillin 1 hour after the dose were sufficient to inhibit *Strept. pneumoniae*, but many strains of *H. influenzae* would not be inhibited. However, it is still not clear how important it is to obtain good sputum levels of antibiotics in the treatment of lower respiratory infections (Lambert 1979), and clearly it is the results of clinical trial that are all important. Amoxycillin has an outstanding success rate in chronic bronchitis (May & Ingold 1972). Judgement on the place of 'Augmentin' in chest infections must await a larger trial in which infecting organisms resistant to amoxycillin but sensitive to 'Augmentin' are found. It is in this type of patient that 'Augmentin' might have a decisive advantage over amoxycillin alone. In the present trial only two patients had such infecting organisms, and neither was eligible for clinical assessment. Elliott et al. (1980) in a trial involving 27 patients had a rather similar experience. We have established, however, that 'Augmentin' is well tolerated and it is certainly preferred by patients to a course of injectable antibiotics.

In future pharmacokinetic studies the knowledge that peak plasma and sputum levels of amoxycillin and clavulanic acid are delayed should be taken into account when planning the investigation.

Acknowledgements

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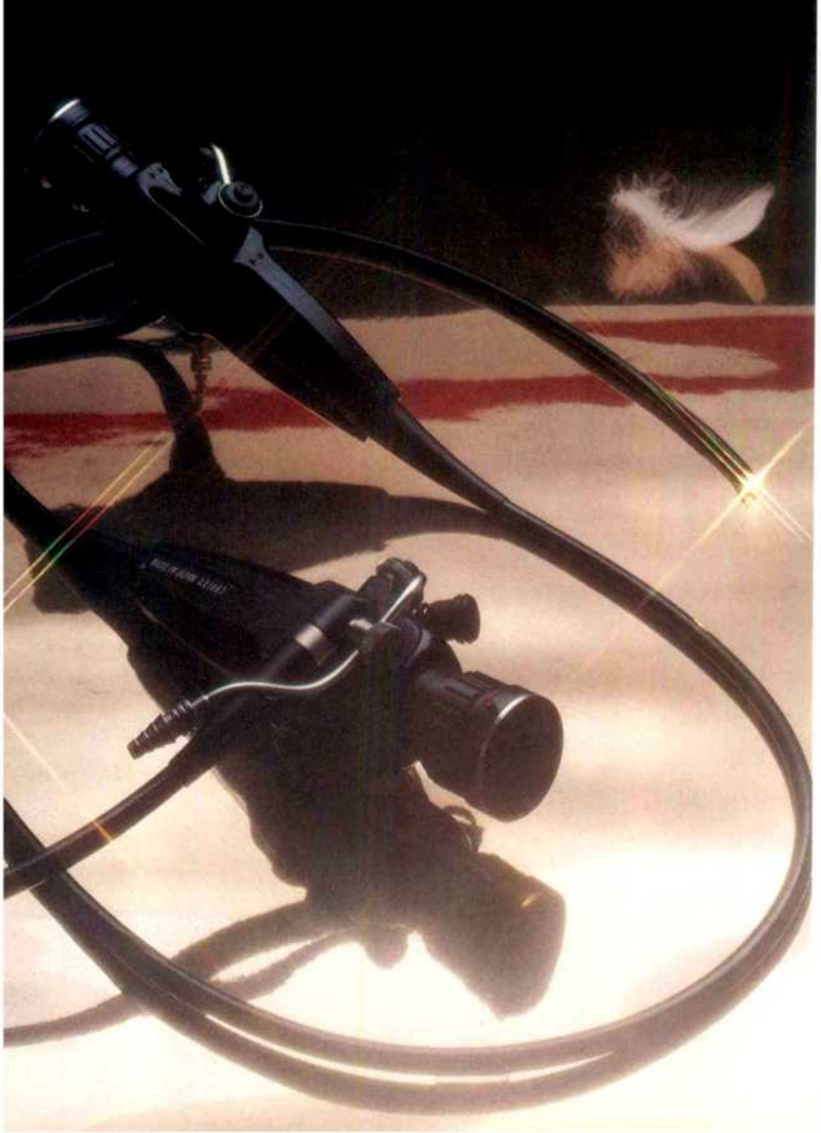

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SUSTAINED-RELEASE THEOPHYLLINE IN CHRONIC BRONCHITIS

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Summary

Twenty-one patients with chronic bronchitis entered a double-blind, cross-over study in which they received sustained-release theophylline ('Nuelin' SA) 350 mg daily for 4 days followed by 700 mg daily for 4 days and matching placebo tablets for 8 days with one week separation.

Seventeen patients completed the study. Three patients receiving higher doses for weight than the mean for the group were withdrawn because of side-effects. Mild side-effects only were reported in six other patients.

Theophylline given twice daily produced a steady-state mean serum concentration of 13.9 μg/ml, 13 patients having concentrations in the range 10–20 μg/ml.

There was no demonstrable improvement of symptoms but pulmonary function measurements in the clinic at the end of active treatment showed a statistically significant improvement in PEFR, 1-second forced expiratory volume and forced vital capacity.

Introduction

The use of theophylline and its derivatives in asthma is well established, but their value in the treatment of chronic bronchitis is less clear and a recent study (Jenkins et al. 1981) suggested they were of no benefit. The present study assesses the effectiveness of sustained-release theophylline ('Nuelin' SA) in chronic bronchitis.

Patients and Methods

Twenty-one patients entered a double-blind, cross-over study. They fulfilled the Medical Research Council criteria for chronic bronchitis (Medical Research Council 1965) and in taking the history particular care was taken to exclude patients with clinical features suggesting bronchial asthma. All were ex-smokers. During the study patients continued inhaled bronchodilators in a fixed dose when these had previously been taken. No patient took corticosteroids. Patients either received 'Nuelin' SA 1 tablet (175 mg) b.d. for four days followed by two tablets (350 mg) b.d. for four days or similar numbers of matching placebo tablets. This incremental dosage has been claimed to reduce minor adverse affects (Weinberger & Hendeles 1979). The order of treatment was randomized. The crossed-over study periods were separated by one week, during which no theophylline products were taken.

At the first visit, patients were given an 8-day supply of medication and a diary. In this diary they recorded, at bed-time, subjective assessment of degree of breathlessness, wheeze and cough during the day. Patients attended the clinic at 0900 hours on day 1 and at 1400 hours on day 8 of each treatment period when measurements were made of PEFR, 1-second forced expiratory volume (FEV_1) and forced vital capacity (FVC). For all lung function tests, three measurements were made and the best recorded. Blood was collected at 1400 hours on day 8 for serum theophylline estimation. Blood samples were taken on day 8 of the placebo week but were not analysed. Plasma theophylline levels were measured using high pressure liquid chromatography. From the diary cards means of patients symptom scores on days 4—7 compared with day 1 were analysed and χ^2 testing was applied.

Mean values for lung function tests on day 1 and 8 of each treatment period were compared using paired *t*-tests. No patients used the inhalers before 0930 hours on the test days.

Results

Twenty-one patients (17 males) entered the study. Their mean age was 58 years (range 34—70 years) and their mean PEFR on entry to the study was 48% of a predicted normal (range 27—74%) (Gregg & Nunn 1973). Four patients failed to complete the study, one because of a confusional state attributed to alcohol withdrawal in an unrecognized alcoholic and three because of side-effects (nightmares in one, headache in one and headache and nausea in one). Six patients experienced nausea or headache but elected to continue the study as the symptoms were mild. All side-effects occurred during active treatment except one patient who experienced insomnia during the placebo week. The mean daily dose of theophylline for the whole group was 9.2 mg/kg (range 6—13.2 mg/kg).

The results of the lung function tests performed in the clinic on days 1 and 8 of each treatment period are shown in Table I. There was no significant difference between active and placebo mean values for any lung function tests on day 1 of the two treatment periods. There were no significant differences between the results of lung function tests on days 1 and 8 of the placebo week. During the theophylline week there was a significant improvement on day 8 when compared with day 1 in all the tests. Comparison of the mean change during the theophylline week with that during the placebo week showed a significant difference in PEFR ($P < 0.05$) and FVC ($P < 0.02$) in favour of theophylline but no significant difference in FEV_1.

Patients' diary scores for treatment and placebo periods were not statistically significantly different at the $P = 0.05$ level. In the 17 patients completing the study the arithmetic mean serum theophylline concentration was 13.9 μg/ml (76.5 mmol/litre) 4½ hours after taking the last dose on day 8. Thirteen patients were within the range 10—20 μg/ml (55—110 mmol/litre). Two had levels of 6 and 8 μg/ml (33 and 44 mmol/litre) and two of 22 and 26 μg/ml (121 and 143 mmol/litre). Of the six patients experiencing mild headache and nausea but continuing the trial only one showed serum theophylline > 20 μg/ml (110 mmol/litre).

Discussion

In bronchial asthma improvement in lung function after theophylline is directly related to the logarithm of the plasma theophylline concentration within the

Table I. Statistical analysis (paired *t*-tests) of pulmonary function data for 17 patients measured on days 1 and 8 of each treatment period

	Active *Day 1*	v *Active* *Day 8*	*Placebo* *Day 1*	v *Placebo* *Day 8*	*Active* *Day 8*	v *Placebo* *Day 8*	*Active* – *Difference between day 8 and day 1*	v *Placebo* – *Difference between day 8 and day 1*
PEFR (litre/min)								
Mean	280.0	304.1	288.2	290.6	304.1	290.6	24.1	– 3.5
+SEM	17.0	19.0	17.4	17.2	19.0	17.2	6.9	10.3
t	–3.5211		0.342		1.179		2.136	
P	< 0.01		n.s.		n.s.		< 0.05	
FVC (ml)								
Mean	2335	2641	2338	2426	2641	2426	323.5	88.2
+SEM	138.1	124.0	127.4	136.5	124.0	136.5	64.8	81.3
t	–4.996		–1.085		4.233		2.801	
P	< 0.001		n.s.		< 0.001		< 0.02	
FEV_1 (ml)								
Mean	1347	1462	1347	1344	1462	1344	114.7	–2.9
+SEM	123.7	104.5	122.2	108.1	104.5	108.1	42.2	66.4
t	–2.72		0.044		2.691		1.757	
P	< 0.02		n.s.		< 0.02		n.s.	

Note. There is no significant difference (n.s.) between *Active* and *Placebo* values for any parameter measured on day 1.

range 5–20 μg/ml (Mitenko & Ogilvie 1973). In the present study in bronchitics the arithmetic mean peak plasma theophylline level was 13.9 μg/ml. Theophylline has a half-life of approximately six hours in adults necessitating unrealistically short dosing intervals to achieve stable blood levels with minimal trough to peak variations. 'Nuelin' SA is a sustained-release preparation with good bioavailability which gives adequate serum theophylline levels with a twice-daily dosage (Svedmyr et al. 1979; Munch et al. 1981).

Side-effects with methylxanthine therapy are usually considered to be associated with relatively high plasma theophylline levels (> 20 μg/ml) and are uncommon at levels below 15 μg/ml (Jacobs et al. 1976). Four of the six patients in our study who experienced mild toxicity had plasma levels < 15 μg/ml. It has been suggested (Ogilvie 1978) that between 5 and 15% of patients do not tolerate oral theophylline even when their plasma concentration is below 15 μg/ml. In the three patients who were withdrawn because of toxic symptoms it was impractical to measure plasma theophylline levels at the time of withdrawal. However, the daily theophylline dosage per kg body weight was higher for those patients than the mean for the group. In chronic bronchitis a study by Jenkins et al. (1981) used daily doses of a slow-release theophylline (Rona Slophyllin 250 mg b.d.) and slow release aminophylline (Phyllocontin 325 mg b.d. ≡ 520 mg theophylline daily). No improvement in PEFR was detected when compared with placebo values. The arithmetic mean plasma theophylline level was 8.7 μg/ml and the mean level in the present study of 13.9 μg/ml seems necessary to achieve improvement in bronchitis. None of the patients experienced toxicity in the study of Jenkins et al. contrasting with the relatively frequent side-effects we noted with a daily dose of 700 mg.

The clearcut improvement in the lung function tests was not accompanied by any detectable improvement in the diary card scores. Possibly patients cannot sense changes in lung function of this order or the form of diary card was not well suited to detect subjective changes.

Acknowledgements

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ASSESSMENT OF OPTIMUM DOSE OF INHALED TERBUTALINE IN PATIENTS WITH CHRONIC ASTHMA: THE USE OF SIMPLE, CUMULATIVE DOSE–RESPONSE CURVES

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Summary

In eight patients with chronic severe asthma, maximal responses to inhaled terbutaline sulphate occurred with between 2 and 5 mg (four to ten times the usual inhaled dose). Forced vital capacity continued to increase with increasing dose of terbutaline in three patients when peak expiratory flow rate (PEFR) and first second forced expired volume (FEV_1) failed to increase further.

We recommend individualizing doses of inhaled bronchodilator in patients with chronic asthma who fail to respond to inhaled β-agonists in normal doses, using simple cumulative dose–response curves, measuring changes in vital capacity in addition to PEFR and FEV_1.

INTRODUCTION

Patients with chronic severe asthma may respond poorly to conventional doses of inhaled β-sympathomimetic agents. Some will achieve more benefit from higher doses delivered either by wet nebulization of respirator aerosol solution (Connellan & Wilson 1978; Prior et al. 1982) or by simple aerosol devices such as the tube-spacer. The purpose of this study was to assess the value of dose–response curves in determining the dose of inhaled bronchodilator which produced maximum improvement of airways obstruction for individual patients.

Patients, Materials and Methods

Eight patients (four male and four female), age range 53–67 years, participated in the study. All had severe airflow obstruction (range of forced expired volume in one second (FEV_1) 0.5–1.6 litres BTPS), but showed diurnal variation in airflow obstruction of 15% or more documented by home recording of peak expiratory flow rate (PEFR) (Prior & Cochrane 1980). Four patients were receiving oral corticosteroids (dose range 10–15 mg/day), all were receiving inhaled salbutamol 200–400 μg four times daily and beclomethasone dipropionate 200–400 μg four times daily. All were non-smokers.

At the time of the study all patients were in a stable clinical condition. Patients were instructed to omit the dose of inhaled bronchodilator before the study. Before starting the study the following were measured: PEFR (using a Wright peak flow meter), FEV_1 and forced vital capacity (FVC) (using a Vitalograph dry spirometer); the best of three readings was recorded. Thereafter, inhaled terbutaline was administered by tube-spacer (using canisters supplied by the manufacturers delivering 1 mg per metered dose) at 30-minute intervals to a maximum cumulative dose of 5 mg. PEFR, FEV_1 and FVC were measured every 15 minutes (best of three attempts). Each patient was asked to note any side effects.

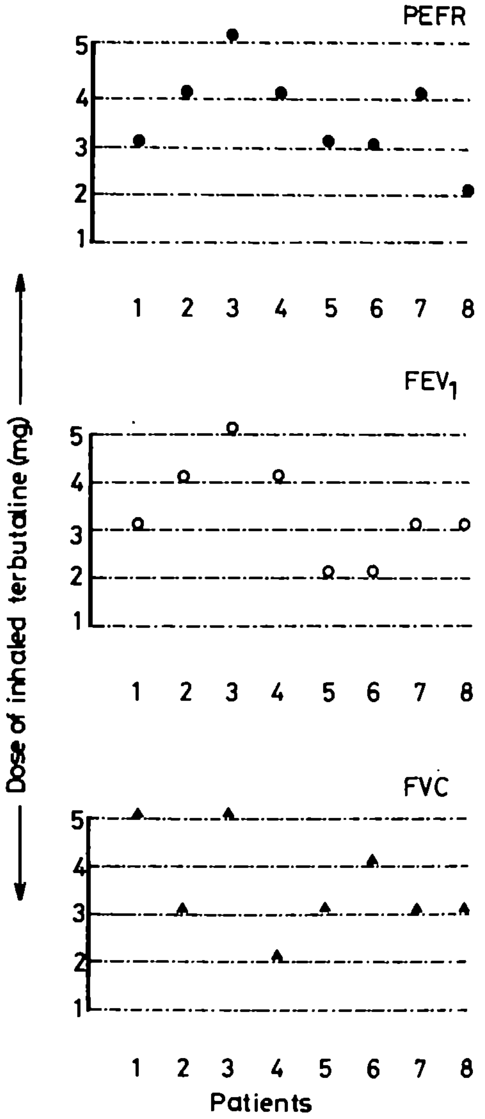

Fig. 1. Doses of terbutaline at which maximum increases in PEFR (top panel), FEV_1 (middle panel) and FVC (lower panel) occurred in the eight patients with chronic asthma

RESULTS

Fig. 1 shows the dose of terbutaline at which the greatest values for PEFR, FEV_1 and FVC were obtained for each patient. The dose which gave maximal improvement in PEFR, FEV_1 or FVC varied between patients. Maximum increase in any one of these measurements occurred at a mean dose of 3.5 mg inhaled terbutaline (range 2–5 mg). In three patients FVC continued to increase with increasing dose of inhaled terbutaline, although PEFR and FEV_1 did not change further. No side effects were noted.

DISCUSSION

Chronic asthma is difficult to treat. Since corticosteroid resistance may occur (Carmichael et al. 1981) it is important to obtain maximal benefit from inhaled bronchodilators. Frequently, however, β_2-sympathomimetic agents are administered in standard dosage with no assessment of response. Even in the laboratory, only a single dose of inhaled bronchodilator is usually given to assess reversibility of airways obstruction and rarely is assessment made of the dose which gives maximum improvement in PEFR, FEV_1 or FVC. Patients with chronic asthma may improve considerably, both subjectively and objectively, on high-dose inhaled bronchodilator (Connellan & Wilson 1978; Prior et al. 1982). Our findings lend support to the idea that in patients whose symptoms are severe or difficult to control the dose of bronchodilator for chronic usage should be determined from simple dose–response studies. Some of our patients gained maximum benefit only after ten times the usual dose of inhaled terbutaline. There was, however, inter-patient variation and it would therefore seem sensible to assess the optimum dose of bronchodilator for each patient.

This study also highlights the importance of measuring forced vital capacity in addition to PEFR and FEV_1. FVC continued to increase with increasing dose of terbutaline in three of the eight patients. If only FEV_1 and PEFR had been measured, the 'optimum' dose of bronchodilator would have been missed in these patients. This may have considerable practical importance, since the 12-minute walking test, a simple measure of disability, correlates much better with FVC than PEFR or FEV_1 (McGavin et al. 1978).

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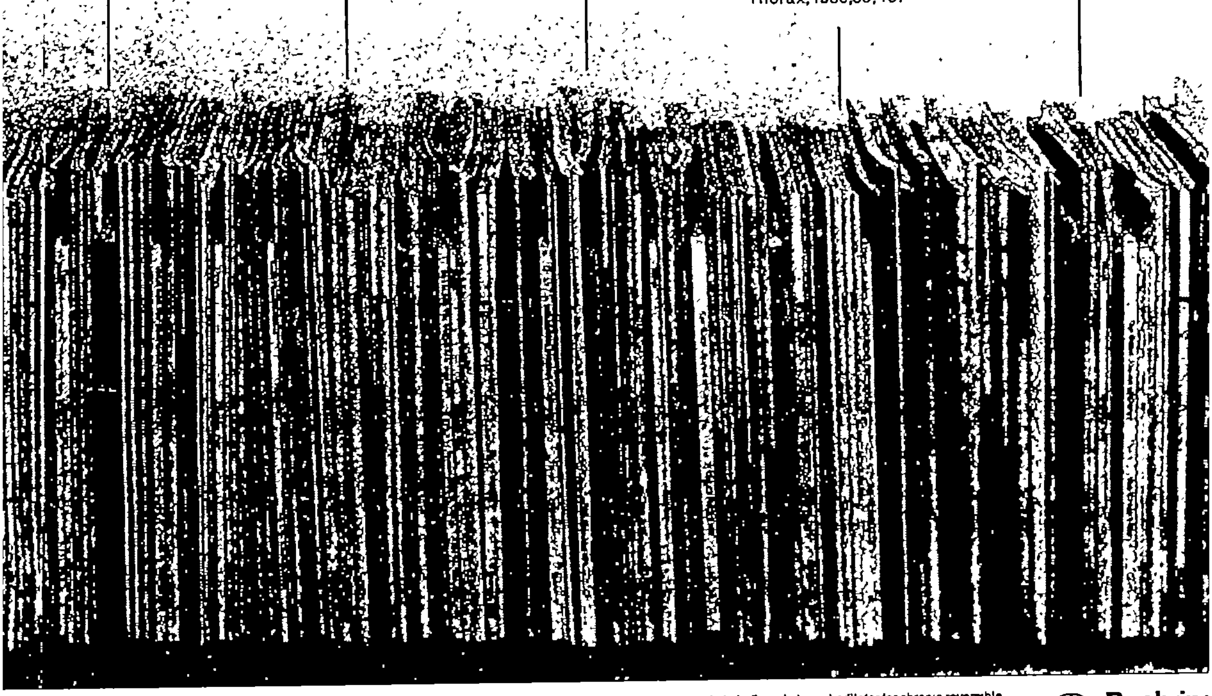

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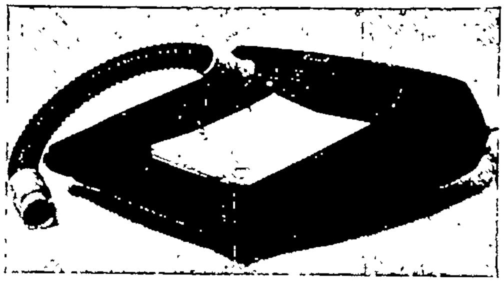

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AN EXERCISE TEST TO ASSESS CLINICAL DYSPNOEA: ESTIMATION OF REPRODUCIBILITY AND SENSITIVITY

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Summary

A new test for assessing clinical dyspnoea with greater precision has been devised. This involves walking on a treadmill while ventilation is measured and dyspnoea is assessed serially with visual analogue scales. The test has been applied successfully in patients with chronic bronchitis and emphysema and in asthmatic patients.

The reproducibility of the test was determined by comparing identical periods of exercise separated by an interval of five days in patients with chronic bronchitis and emphysema. The relationship between dyspnoea score and ventilation showed acceptable within-patient reproducibility.

The sensitivity of the test was investigated in asthmatic patients by comparing exercise after placebo and after salbutamol which had increased PEFR by a mean of 33%. After salbutamol, lower breathlessness scores usually occurred for a given level of ventilation and this indicates that the test was sensitive enough to detect an effective treatment.

Thus more precise assessment of dyspnoea in patients is feasible and generally reliable. However a proportion of patients respond unpredictably and it is necessary to apply this test critically and with an appreciation of its limitations.

Introduction

Over the last few years there has been increasing interest in drugs which might alleviate the distress of dyspnoea in patients with severe irreversible respiratory disease. Guz and his colleagues (Mitchell-Heggs et al. 1980) gave diazepam chronically to four pink puffer patients and found a reduction in dyspnoea and an increase in the tolerance of exercise. In their study, the severity of dyspnoea was determined from the patient's verbal account. Detection of subtle drug effects would require a more precise means of assessing breathlessness. Accepting that dyspnoea is subjective with no satisfactory objective substitute, Stark and Gambles (1980*b*) showed in healthy subjects that visual analogue scales (VAS) could be employed to assess breathlessness and that the relationship of breathlessness score to ventilation showed satisfactory within-subject reproducibility. Introduction of low value respiratory resistance altered this relationship and caused greater breathlessness in relation to ventilation, which demonstrated that the method had adequate sensitivity (Stark, Gambles & Lewis 1981). Using such methods they found that rebreathing carbon dioxide caused greater breathlessness than exercise in normal volunteers (Stark & Gambles 1980*a*; Gambles & Stark 1981). These findings were later confirmed by Guz et al. (1981) who showed in addition still greater breathlessness induced by hypoxia. A different approach to assessment using numbers rather than VAS was described by Killian et al. (1981) to estimate loads applied to breathing. Of the drugs tested in healthy subjects many have not affected breathlessness (e.g. Stark & Gambles 1981) although promethazine caused a minor reduction in breathlessness during exercise but not during exposure to raised levels of carbon dioxide (Stark & Gambles 1980*a*; Stark, Gambles & Lewis 1981).

The logical extension of this work is to apply the methods to the assessment of dyspnoeic patients. Woodcock et al. (1981*a*) used VAS to study breathlessness during exercise in pink puffer patients. Administration of oxygen reduced breathlessness scores during exercise but it is not known whether similar levels of ventilation were attained. More recently they have extended the work on promethazine to patients and have found a small but statistically significant reduction in breathlessness compared to placebo or to diazepam (Woodcock et al. 1981*b*).

It seems likely that the relatively simple methodology which has been developed will be used to examine the effects of drugs on breathlessness in different disease states, and we believe that it is important to subject the methods to critical appraisal in patients at an early stage.

This report describes the assessment of breathlessness during exercise in two groups of patients and looks particularly at the reproducibility and the sensitivity of the test system. Reproducibility was studied in patients with chronic bronchitis and emphysema who performed identical periods of exercise and was expressed in terms of the relationship between dyspnoea and ventilation. Preliminary results have been presented previously (Stark, Gambles & Chatterjee 1981). The demonstration of sensitivity in the method requires induction of rapid improvement in breathlessness without major effects on ventilation, and for this reason, we studied asthmatic patients before and after treatment with salbutamol.

It is hoped that this information will provide a useful basis for future studies on the effects of drugs on dyspnoea.

Methods

Exercise

Dyspnoea was induced by walking on a treadmill. The patients studied had limited exercise tolerance and the angle of incline and the speed suitable for each patient were determined in preliminary tests. Exercise generally continued for 4 minutes with 2 minutes at each of two speeds but in several patients shorter periods of exercise had to be used. All patients were able to stop the treadmill if they so wished.

Physiological measurements

Respiration was measured by passing the expired gas through a pneumotachograph (Fleisch head no. 3) and then through a mixing cone from which gas was sampled for measurement of oxygen (Morgan 252 D paramagnetic oxygen analyser) and carbon dioxide (Morgan 801 infrared carbon dioxide analyser). The outputs from the pneumotachograph and from the gas analysers were recorded continuously on a Gould 2600 chart recorder and in addition a microprocessor presented corrected data ($\dot{V}O_2$, STP; $\dot{V}_E$, V_T, f_R, BTPS) at intervals of 1 minute. ECG was monitored continuously and heart rate was derived from this. Calibration preceded every study.

As in our earlier studies on healthy subjects, the patients were connected to the system using a tight-fitting face mask (Martindale MP-3 or Gold Cross Protector BS 2091). Inspiration was from the atmosphere through a low resistance valve and expiration was through the pneumotachograph. During each study, checks were made to ensure that leaks were not occurring by sampling for CO_2 at the periphery of the mask.

Peak expiratory flow rate (PEFR) was measured with a Wright peak flow meter before and after treatment and after exercise. In this way, any effect of exercise or the test drugs on bronchomotor tone could be detected.

Breathlessness

Visual analogue scales (VAS) were administered at rest before exercise, during exercise and during the period of recovery. The maximum point on the VAS was anchored by relating it to an activity the patient undertook in his daily life and which induced breathlessness of a severity which was easily recalled by the patient. During the tests environmental factors were controlled as far as possible and comparisons were made only on a within-subject basis.

The VAS were administered at intervals of 1 minute by a PET Commodore Computer connected to a television screen suspended in front of the patient. His response was made using finger controls. A straight line measuring 20 cm was presented to the patient with the minimum point labelled 'not at all breathless' and the maximum point labelled 'very breathless'. Each patient received careful instruction on use of the VAS and had at least one complete trial run before any test was conducted.

Patients and protocol

Reproducibility. For this study, five patients with chronic bronchitis and emphysema were recruited. All patients gave written informed consent and the study was approved by the Hospital Ethical Committee. Clinical information on the patients is provided in Table I. They had evidence of irreversible airways obstruction with a low or normal $PaCO_2$ and breathlessness on moderate exertion. All were dyspnoeic during activities such as climbing one to three flights of stairs, and four had retired prematurely because of respiratory limitation. Only one of the patients was currently a smoker and he abstained from smoking for 2 hours before each of the tests.

Patients attended the hospital laboratory on three occasions. The first was for familiarization and the next two were separated by 5 days. Identical exercise tests were undertaken on these occasions and the relationship of dyspnoea to ventilation was compared for each subject.

Sensitivity. Five male patients with wheeze and intermittent obstruction of the airways characteristic of bronchial asthma agreed to participate in this investigation after demonstration of an improvement in FEV_1 following inhalation of bronchodilator aerosol (Table I). Sensitivity was tested during a single session in the laboratory which lasted 2–3 hours. This was preferred to a study covering several days because of the possibility of changes in clinical status. After a familiarization run, the patients undertook two identical exercise tests one 20–30 minutes after a placebo aerosol and the other 20–30 minutes after 200–300 μg of salbutamol by aerosol. Therapeutic salbutamol was withheld on the day of study but other treatments continued as usual. Because of the duration of action of salbutamol it was not possible to randomize the order of the treatments.

Results

Exercise test

All the patients included in this study were able to walk on the treadmill although the load and duration varied considerably from patient to patient and was much lower than reported previously in healthy subjects (Stark, Gambles & Lewis 1981). Patients usually tolerated the face mask but in several the mask caused an increase in ventilation and breathlessness score even in the absence of exercise. The method of recording VAS was understood by the patients.

Table I. Clinical information on patients with chronic bronchitis participating in test of reproducibility and on asthmatic patients in test of sensitivity

	Pt 1	*Pt 2*	*Pt 3*	*Pt 4*	*Pt 5*
Reproducibility					
Age, sex	60,M	67,M	52,M	62,M	66,M
Height (cm)	172	162	167	160	172
Weight (kg)	77	64	67	70	58
FEV_1 (litres)	1.3	0.8	2.4	1.5	1.1
VC (litres)	2.9	2.7	3.7	2.8	2.7
FEV_1/VC (%)	45	30	65	54	41
RV/TLC (%)	55	54	52	50	58
Transfer factor (ml CO/min/mm Hg)	29.2	11.0	21.7	27.0	20.3
PaO_2 (kPa)	9.2	8.1	10.1	9.3	9.2
$PaCO_2$ (kPa)	5.1	5.6	4.9	5.5	4.9
Sensitivity					
Age, sex	46,M	52,M	16,M	23,M	59,M
Height (cm)	187	174	175	167	170
Weight (kg)	83	73	56	73	80
Positive skin prick tests	+	—	+	+	+
FEV_1 (litres)	3.1	2.4	2.3	2.5	1.5
FEV_1 after br.dil. (litres)	3.9	2.9	3.0	3.0	1.9
VC (litres)	5.7	5.3	4.0	3.8	3.1
FEV_1/VC (%)	54	45	58	66	48
PaO_2 (kPa)	10.8	11.9	12.0	9.9	9.6
$PaCO_2$ (kPa)	5.1	5.3	5.1	4.7	5.1
Treatment salbutamol	+	+	+	+	+
beclomethasone	+	+	+	+	+
prednisolone	+	—	—	+	—
theophylline	—	—	+	+	—

Reproducibility

First it was necessary to establish that the patients were in a similar condition on the two days of study and that the physiological responses to exercise were similar. PEFR was not significantly different for the group although some individuals (e.g. patient 2) showed differences. The values for heart rate and oxygen uptake at rest and during the final minute of exercise were similar during the two tests (Table II).

Fig. 1 shows the responses of the first patient. During exercise there was an increase in ventilation which was accompanied by an increase in dyspnoea score. When exercise ceased both ventilation and dyspnoea score returned towards the base-line values over a period of 4 min. The responses during the two tests showed marked similarity. In Fig. 2 the relationships between dyspnoea score and ventilation are shown for all five patients. In patients 1, 4 and 5 adequate reproducibility was demonstrated. Patient 3 showed a rise in ventilation in response to wearing the mask and this was greater during the first test. However, at the maximum value of ventilation common to both tests, similar dyspnoea scores obtained. Patient 2 used only the lower end of the VAS but the dyspnoea score during the second test was only half that during the first and it is noteworthy that this patient showed a higher PEFR on this occasion (Table II).

Table II. Comparability of exercise tests for studies on reproducibility and sensitivity

			Pt 1	*Pt 2*	*Pt 3*	*Pt 4*	*Pt 5*	*Mean* ± SE
Reproducibility								
PEFR	Day 1	pre-ex.	180	125	395	245	145	218 ± 39.8
(litres/min)	Day 5	pre-ex.	175	160	380	220	180	223 ± 33.1
Heart rate	Day 1	basal	84	71	83	77	86	80.2 ± 2.75
(beats/min)		max.	113	99	91	101	104	101.6 ± 3.57
	Day 5	basal	81	76	80	68	83	77.6 ± 2.65
		max.	113	98	90	90	103	98.8 ± 4.33
$\dot{V}O_2$	Day 1	basal	331	349	345	348	321	339 ± 5.5
(ml/min)		max.	1380	854	735	657	898	905 ± 126.3
	Day 5	basal	382	290	292	319	308	318 ± 16.8
		max.	1525	828	730	645	770	900 ± 158.8
Sensitivity								
PEFR	Placebo	pre-ex.	370	230	435	245	230	302.0 ± 42.4
(litres/min)		post-ex.	375	280	340	210	220	285.0 ± 32.4
	Salbutamol	pre-ex.	485	355	515	385	270	402.0 ± 44.5
		post-ex.	485	370	500	420	320	419.0 ± 34.0
Heart rate	Placebo	basal	97	81	104	84	79	89.0 ± 4.89
(beats/min		max.	128	118	127	104	114	118.2 ± 4.43
	Salbutamol	basal	98	81	94	87	83	88.6 ± 3.06
		max.	135	118	116	100	109	115.6 ± 5.78
$\dot{V}O_2$	Placebo	basal	444	290	307	265	315	324.2 ± 31.2
(ml/min)		max.	2202	1527	1260	1098	1344	1486.2 ± 191.8
	Salbutamol	basal	416	274	295	272	362	323.8 ± 28.2
		max.	2230	1750	1108	1114	1362	1512.8 ± 214.0

Pooling of the data from these patients was difficult because of the varying periods of exercise. In the final panel of Fig. 2 is shown the mean resting value and the mean value in the final minute of exercise. This reveals close similarity of response during the two tests consistent with adequate reproducibility.

Sensitivity

After treatment with placebo the PEFR averaged 302 litres/min and after salbutamol the base-line PEFR was 402 litres/min which represents a 33% improvement. Heart rate and oxygen uptake both at rest and during the final minute of exercise were similar for the placebo and salbutamol tests (Table II).

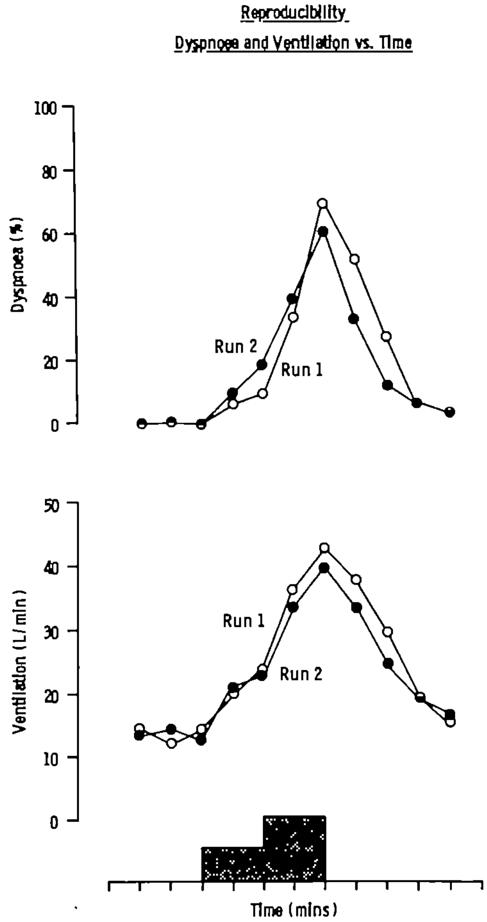

Fig. 1. The changes in dyspnoea score and ventilation in a patient with chronic bronchitis and emphysema during two identical periods of exercise

The response of the first patient is shown in Fig. 3. In the presence of salbutamol, PEFR increased from 370 to 485 litres/min and the breathlessness scores during exercise were depressed although ventilation was unchanged. In Fig. 4 are shown the responses of the five patients and the mean for the group. The test was sufficiently sensitive to demonstrate a drug-induced effect in three of the five patients. In one patient (no. 4) the responses were alike for placebo and salbutamol and this was consistent with his overall impression that the breathlessness was similar during the two tests. In another patient (no. 3) greater breath-

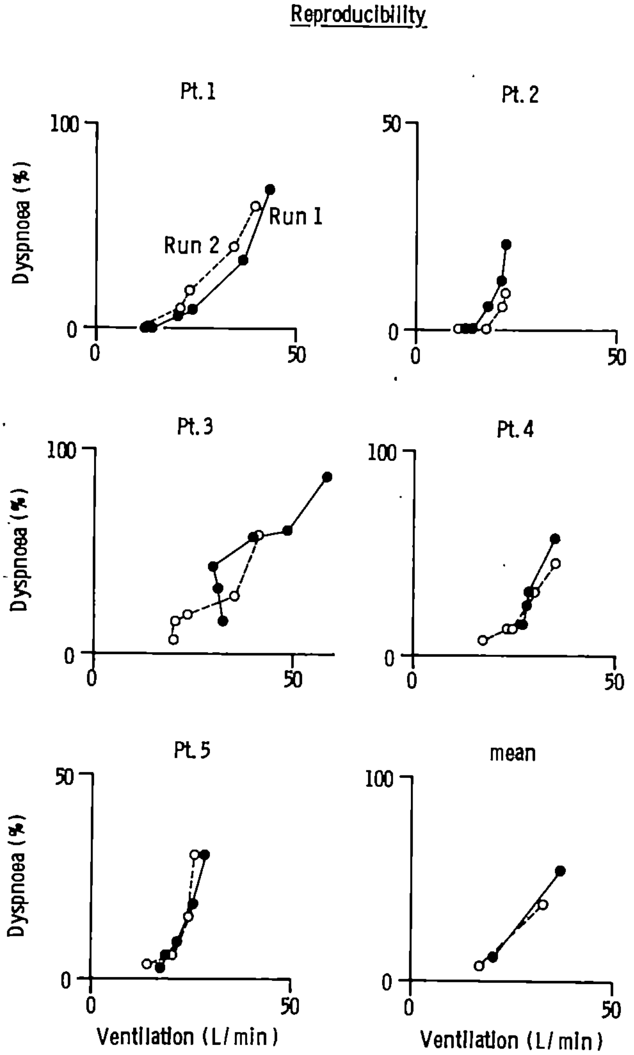

Fig. 2. The relationship between dyspnoea score and ventilation in five patients with chronic bronchitis and emphysema during two identical periods of exercise

lessness was recorded in the presence of salbutamol in spite of his general comment that he was less short of breath after the second treatment (salbutamol). The mean response for the group was consistent with sensitivity.

Discussion

Our present studies have shown that it is possible to assess clinical dyspnoea with precision using a test which does not take the patient to the limit of his tolerance. VAS provide the means for observing the onset and development of dyspnoea as well as the recovery after exercise. The VAS has, of course, the limitations of any subjective assessment but in the study of a symptom there is no clear alternative. Our efforts therefore have focussed on devices to increase the reliability of these methods and on exploration of their limitations. Patients used the VAS in an individual fashion which probably related to psychological make-up and attitude to their disease as well as to the severity of their disability in relation to the exercise. Any comparison to assess response to a treatment should therefore be made on a within-subject basis, provided that the clinical condition of the patient is similar and that there is control of environmental factors.

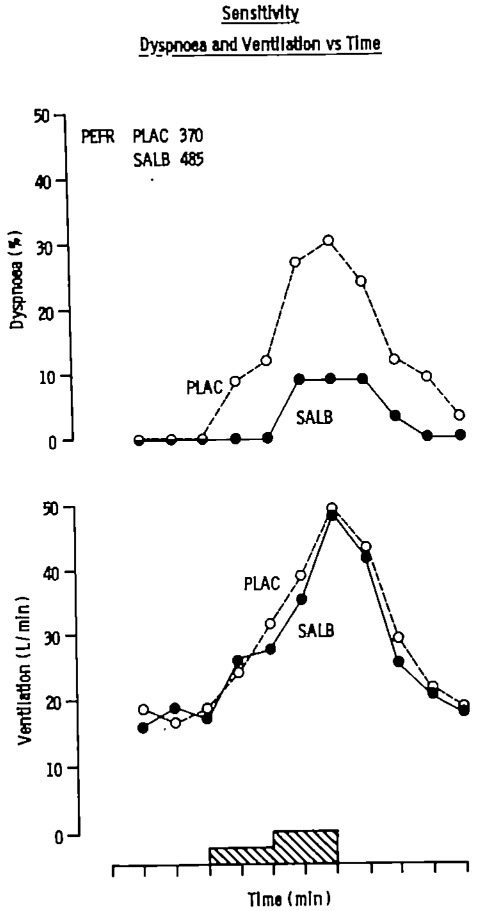

Fig. 3. The changes in dyspnoea and ventilation in an asthmatic patient during exercise after placebo and after salbutamol

In our previous study on healthy subjects (Stark, Gambles & Lewis 1981), the maximum point on the VAS was anchored at the start of each test by a short period of strenuous exercise. In view of the limited exercise tolerance of the patients we did not feel that this approach was justifiable, and indeed the resulting fatigue might have detracted from the subsequent tests. Instead the patient fixed the 100% mark on the VAS by reference to a familiar activity in his daily life (see *Methods*). Other workers have found acceptable reproducibility in the estimation of breathlessness in normal subjects without any attempt at anchoring (Guz et al. 1981).

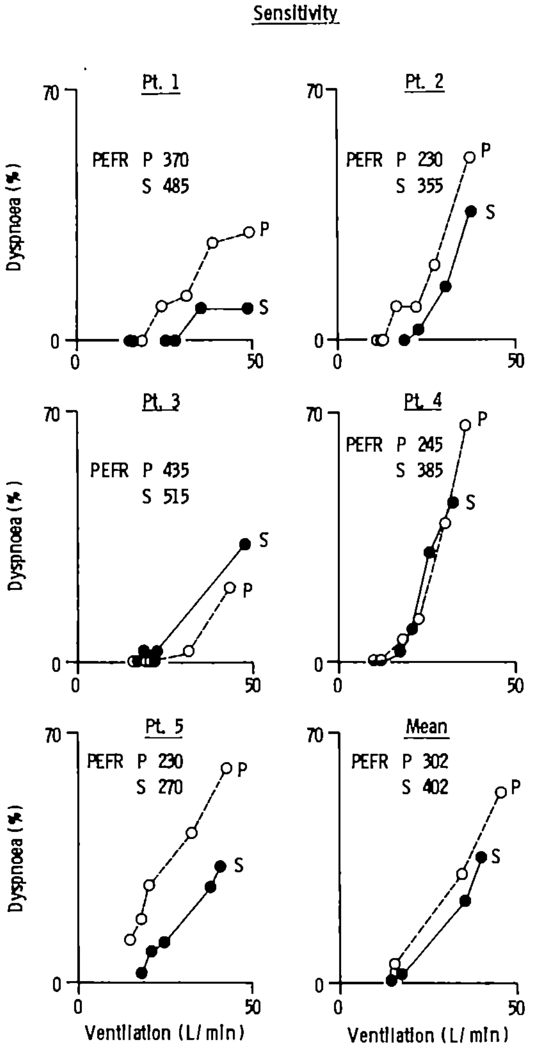

Fig. 4. The relationship between dyspnoea score and ventilation in five asthmatic patients during exercise after placebo and after salbutamol

No attempt was made to reach a steady state during exercise since the aim was to achieve a range of values for ventilation. A progressive test might have been a suitable alternative. We have chosen to express the responses of patients by the relationship between the dyspnoea score and ventilation since this had proved useful in the studies on healthy subjects (Stark, Gambles & Lewis 1981). A treatment which benefited dyspnoea would therefore be expected to move the curve towards the ventilation axis and this might occur either during exercise or during recovery.

The results indicate that the dyspnoea/ventilation plot is generally reproducible and is capable of being modified by a drug which reduces breathlessness. The patients in the study were selected for their co-operation and understanding and it is likely that unselected patients would show less consistency in their use of the VAS. In spite of our efforts, some patients did use the VAS in a way which suggested either poor reproducibility or insensitivity and in studies on the effects of drugs, patients participating should undergo checks to ensure that the VAS is being used in a meaningful way.

Acknowledgements

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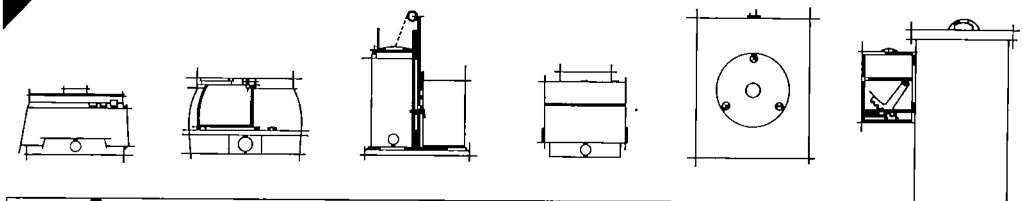

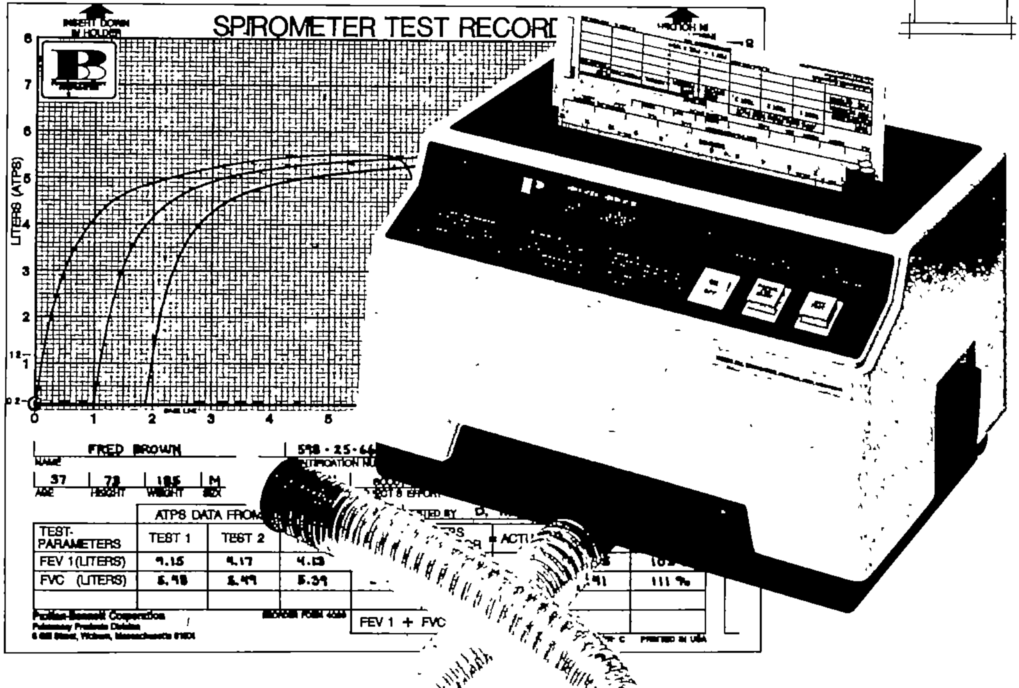

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LITERS (ATPS)

FRED BROWN				598 · 25 · 6
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AGE	HEIGHT	WEIGHT	SEX	

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	ATPS DATA FROM		
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FVC (LITERS)	5.48	5.49	5.39

FEV 1 ÷ FVC

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ERRORS IN THE ESTIMATION OF VITAL CAPACITY FROM EXPIRATORY FLOW–VOLUME CURVES IN PULMONARY EMPHYSEMA

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Summary

Patients with radiological evidence of pulmonary emphysema performed forced and relaxed inspiratory and expiratory flow–volume (FV) curves to assess the accuracy of vital capacity (VC) measurement, using two systems, an integrating pneumotachograph and a differentiating spirometer.

Study 1

Sixteen patients performed the FV curves using the pneumotachograph system only. Forced inspiratory VC (F-IVC) was greater than forced expiratory VC (F-EVC) by 0.61 litres ($P < 0.001$) and relaxed inspiratory VC (R-IVC) was greater than relaxed expiratory VC (R-EVC) by 0.88 litres ($P < 0.001$).

Study 2

Ten patients performed the same manoeuvres using the two measurement systems. F-IVC was greater than F-EVC ($P < 0.001$) in both systems, the discrepancy being larger on the pneumotachograph system.

Two errors arise during performance of EVC in emphysema, which would lead to underestimation of VC: (a) a physiological error resulting from dynamic airway compression and affecting forced manoeuvres in particular, (b) a technical error affecting the pneumotachograph system in use and due to failure of the integrator to record volume at low flow rates. Indices derived from F-EVC curves such as maximal expiratory flow at 50% VC would also be subject to error in patients with emphysema.

Introduction

The maximal inspiratory and expiratory flow–volume (FV) curve has been extensively used following its introduction by Fry and Hyatt (1960). While helpful information can be obtained from its shape, the curve, particularly the expiratory limb, can also be used to obtain maximal flow rates at a given fraction of the vital capacity (VC). These indices have been employed as diagnostic criteria and for assessment of respiratory disability and bronchodilator responsiveness.

If useful information is to be obtained by this method, it is clear that the forced expiratory VC must represent an accurate and reproducible volume; in pulmonary emphysema, however, it has been shown by spirometry that the forced VC is often markedly less than the VC obtained by a relaxed manoeuvre (Hutchison et al. 1973). One would therefore expect that the VC derived from the maximal expiratory FV curve would be subject to similar errors, and during preliminary observations using a commercial pneumotachograph and integrator system in emphysematous patients it became clear that such errors were indeed occurring.

The following study was therefore carried out to ascertain firstly what effect such an error might have upon the quantitative measurements obtainable from a maximal expiratory FV curve and secondly to compare the two commonly used methods, the integrating pneumotachograph and the differentiating spirometer.

Patients and Methods

Twenty-four male subjects with radiological evidence of pulmonary emphysema (Laws & Heard 1962) were studied. Forced expiratory volume in one second (FEV_1) and VC were measured on a Bernstein spirometer, total lung capacity (TLC) and residual volume (RV) using the Collins complete body plethysmograph system 09001 and transfer factor (tCO) and transfer coefficient (kCO) using the Morgan Model C transfer test. The predicted values were obtained from tables prepared by Cotes (1975).

Study 1

Sixteen subjects performed FV curves using a Collins complete body plethysmograph system 09001 with a heated Fleisch No. 3 pneumotachograph ('Pneumo' system). The curves were displayed on an oscilloscope and photographed for measurement.

Two types of FV curve were performed:

1. Forced manoeuvres

Forced inspiratory VC (F-IVC): the subject first breathed at tidal volume then exhaled slowly to RV. When no further airflow was observed the subject inhaled at maximal rate to TLC.

Forced expiratory VC (F-EVC): From TLC the subject performed the forced expiratory manoeuvre.

The greatest F-IVC and F-EVC from three attempts were analysed.

2. Relaxed manoeuvres

Relaxed inspiratory VC (R-IVC): The subject exhaled slowly to RV and then inhaled slowly to TLC.

Relaxed expiratory VC (R-EVC): After reaching TLC the subject exhaled in a relaxed manner as far as possible.

The greatest of three R-IVC and R-EVC manoeuvres were recorded.

Study 2

Ten subjects, two of whom had already performed study 1, took part in study 2. FV curves were performed on the 'Pneumo' system as in study 1 and also using a Morgan flow–volume differentiator ('FV Diff') connected to an 8-litre rolling seal dry spirometer (P.K. Morgan) and 7045a Morgan/Bryan X-Y recorder. The forced manoeuvre as described in study 1 was performed on the 'Pneumo' system then repeated five minutes later using the 'FV Diff'. The greatest of three attempts on each equipment system was taken for analysis.

Statistics: probability values were obtained by the paired *t*-test.

Results

The mean age and lung function of the 24 subjects are shown in Table I.

Table I. Lung function data as percentage of predicted normal value*

	Study 1 ($n = 16$)		*Study 2* ($n = 10$)	
	Mean	SD	Mean	SD
Age (years)	59	5	58	9
FEV_1	46	22	42	23
VC	79	16	77	15
RV	203	52	208	41
TLC	123	17	131	20
tCO	62	27	51	25
kCO	70	22	66	24

All values are post-bronchodilator
*Cotes (1975)

Study 1

F-IVC, R-IVC, F-EVC and R-EVC from the 16 subjects who performed the first study are shown in Table II. On average, F-IVC was significantly greater than F-EVC ($P < 0.001$), by 0.61 litres; likewise R-IVC was significantly greater than R-EVC ($P < 0.001$), by 0.88 litres. There was no significant difference ($P > 0.05$) between F-IVC and R-IVC nor between F-EVC and R-EVC.

Study 2

F-IVC and F-EVC from the ten subjects who took part in the second study are shown in Table III.

Influence of manoeuvre. The mean difference between F-IVC and F-EVC was 0.25 litres using the 'FV Diff' system and 0.69 litres using the 'Pneumo' system. Both these differences are highly significant ($P < 0.001$).

Influence of equipment. F-EVC was significantly greater ($P < 0.02$) measured with the 'FV Diff' than with the 'Pneumo' system (mean difference 0.39 litres). For F-IVC, there was no difference between the two systems.

Equipment calibration

The volume signal from the 'Pneumo' system was measured using a rotameter at various flow rates. Integration of flow was accurate and linear at flow rates from 12 litres/sec down to 0.15 litres/sec, but below this flow no volume signal was detected. The volume output of the spirometer was linear as tested with an accurately machined syringe. Flow rates were accurate down to 0.015 litres/sec.

Table II. Study 1: VC (litres BTPS) measured from FV curves using the pneumotachograph and integrator system

Patient	*Forced*		*Relaxed*	
	F-IVC	F-EVC	R-IVC	R-EVC
1	3.6	3.0	3.6	2.2
2	3.0	2.3	3.0	2.0
3	3.8	3.1	4.1	3.5
4	4.4	4.0	4.7	3.1
5	3.3	2.8	3.0	2.7
6	3.3	2.2	3.6	1.7
7	4.5	3.7	4.9	4.1
8	4.1	4.1	4.2	3.7
9	3.5	3.2	3.3	2.3
10	2.6	1.9	2.8	2.0
11	3.3	2.2	3.3	2.3
12	3.3	3.0	3.4	3.3
13	5.1	5.1	5.4	4.8
14	3.9	2.8	3.7	3.1
15	4.3	3.9	4.7	3.9
16	3.7	2.7	3.9	2.8
Mean	3.73	3.12	3.85	2.97
Mean difference (IVC minus EVC)	0.61		0.88	
SD of difference	0.36		0.47	
*P**	< 0.001		< 0.001	

There was no significant difference ($P^* > 0.05$) between F-IVC and R-IVC *nor* between F-EVC and R-EVC.

**P*: probability that groups differ by paired *t*-test.

Discussion

It has been known for many years (Gilson & Hugh-Jones 1949) that, in emphysematous patients, a forced expiratory manoeuvre may give a figure for the vital capacity which is too low. Hutchison et al. (1973) similarly observed that the F-EVC in emphysema was substantially less than the IVC and less than the EVC measured by the 'slow' (or 'relaxed') method.

In the present study 1, using a commercial pneumotachograph and integrator system, we obtained similar results and showed again that in the majority of emphysematous patients the F-EVC was considerably lower than the IVC. This discrepancy (of over 1 litre in some cases) is thought to be principally due to the high positive intrapleural pressure produced by the forced manoeuvre leading to dynamic airways compression and premature closure of lung units which would otherwise remain patent. This means that in emphysema RV can very seldom be reached after a forced expiratory manoeuvre from TLC nor is it possible to circumvent this problem simply by reversing the order of the procedure. Thus, if the subject were to perform a slow inspiration to TLC (which poses no difficulty in emphysema), followed by F-EVC and return to TLC then the measured EVC and IVC would be equal – but erroneously low. If flow–volume curves in emphysema are to be correctly assessed, therefore, the IVC should be performed first, after slow exhalation from FRC to RV, to ensure that a true base-line VC is established.

Table III. Study 2: F-IVC and F-EVC (litres BTPS) measured on 'FV Diff' and 'Pneumo' system

Patient	*F-IVC*		*F-EVC*	
	'FV Diff'	'Pneumo'	'FV Diff'	'Pneumo'
1	3.5	3.5	3.3	2.0
2	3.8	3.7	3.5	3.4
3	2.1	2.0	1.8	1.6
4	2.1	1.9	1.9	1.8
5	3.1	3.2	2.9	2.7
6	2.6	2.6	2.4	2.0
7	2.6	2.6	2.3	1.7
8	3.1	3.0	2.9	2.3
9	3.1	3.2	3.0	2.6
10	2.4	3.2	1.9	1.9
Mean	2.84	2.89	2.59	2.20
SD	0.57	0.60	0.61	0.56

We observed in study 1, however, that the *relaxed* EVC was also a good deal lower than the IVC, a discrepancy that seems less readily explained than the underestimate of *forced* EVC on the grounds of airway compressibility.

We had previously noted that the pneumotachograph/integrator system often failed to record a volume signal during the latter part of expiration (Fig. 1) and we therefore undertook a further series of observations (study 2) in order to compare this method with a spirometer linked to a flow–volume differentiator. With the latter system, we found that the F-EVC was again lower than the F-IVC, by an average of 0.25 litres; using the pneumotachograph system, however, the discrepancy was over twice as large. On direct comparison of the two systems, there was no difference in F-IVC but for F-EVC the pneumotachograph system gave substantially lower results than the FV differentiator.

We have obtained evidence, therefore, of two important factors which may affect expiratory VC in patients with emphysema – firstly dynamic compression of the airways which particularly affects the forced expiratory manoeuvres, and secondly a technical factor arising in the pneumotachograph/integrator system itself which applies to both forced and relaxed expiratory manoeuvres. The two factors summate when the F-EVC is performed with the pneumotachograph. The technical error arises from the failure of the system to carry out the integration process when flow falls below 0.15 litres/sec. It may well be therefore that under these conditions the 'true' or maximal value for VC is never recorded in emphysematous patients during the F-EVC. The FV differentiator system records volume directly and is therefore not subject to this error, the differentiated flow signal being accurate down to 0.015 litres/sec. The performance of the pneumotachograph system could no doubt be improved by substituting a more sensitive transducer, but the accuracy of peak flow measurements could then be affected instead. These errors also apply to flow indices derived from the maximal expiratory FV curve at say, 50% of VC ($V_{max_{50}}$); these flow indices would be overestimated if VC was spuriously low, though the error would be small in cases as severe as that illustrated in Fig. 1. $V_{max_{50}}$ and similar indices are on occasion used to assess bronchodilator responses in emphysema. It has been shown that VC in emphysema can be considerably enlarged by inhalation of bronchodilator aerosol (Bellamy & Hutchison 1981); interpretation of changes in $V_{max_{50}}$ in terms of bronchodilator responsiveness would thus be rendered difficult by the fact that

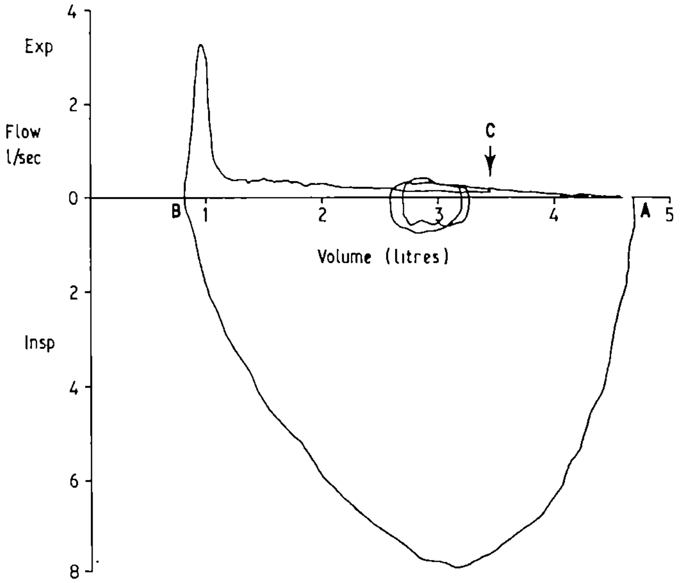

Fig. 1. Maximal inspiratory and expiratory FV curves in a patient with severe emphysema, performed using pneumotachograph/integrator system. (Traced from X-Y recorder chart). The subject (patient 14, study 1) breathed first at normal tidal volume, exhaled to RV (point A), inhaled at maximal rate to TLC (point B) and finally exhaled at maximal rate to point C. The apparent VC estimated from the expiratory FV curve (i.e. distance BC) is 2.8 litres whereas the VC estimated from the inspiratory FV curve (distance AB) is 3.9 litres

the index is measured at different lung volumes and that, in addition, measurement of these volumes may be subject to both physiological and technical sources of error.

Acknowledgements

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ANTITUBERCULOSIS DRUG LEVELS AFTER JEJUNOILEAL BYPASS

T. M. GRIFFITHS, P. THOMAS AND I. A. CAMPBELL
Sully Hospital, South Glamorgan

Summary

After jejunoileal bypass, oral therapy with isoniazid and ethambutol achieves satisfactory blood levels, but it would seem prudent to monitor levels of rifampicin in these patients and adjust dosage as necessary.

Introduction

The incidence of tuberculosis is increased in patients with jejunoileal bypass for obesity, even by as much as sixtyfold (Pickleman et al. 1975; Bruce & Wise 1977). We describe treatment of such a patient with oral rifampicin, ethambutol and isoniazid, treatment being monitored by measurement of serum levels of these drugs.

Methods

All drugs were given shortly after waking and approximately 30 minutes before the first meal of the day. Rifampicin levels were assayed by the *Sarcina Lutea* Columbia Blood Agar method (Dr M. Emerson, Whittington Hospital – personal communication). Isoniazid levels were assayed colorimetrically (Dymond & Russell 1970) and ethambutol by electron capture gas chromatography following derivatization with trifluoaceticanhydride (Dr J. Berry, Poisons Unit, New Cross Hospital – personal communication).

Case Report

The patient, a 48-year-old obese housewife, had a complicated history. At the age of 12 she survived tuberculous meningitis. Between 1962 and 1972 primary amenorrhoea, recurrent fractures and diabetes insipidus led to a diagnosis of partial hypopituitarism. Skull radiograph showed extensive suprasellar calcification. Until 1973 she received chlorpropamide, antidiuretic hormone and oestrogens. Her obesity was attributed to hypothalmic involvement. In 1972, fasting reduced her weight from 120 kg to 114 kg, her height being 145 cm. By 1973 her weight had increased to 130 kg and severe osteo-arthrosis of the knees had developed. In 1974, lipectomy and end-to-side jejunoileal bypass were performed, anastomosing a point 35 cm from the duodenal–jejunal flexure to a point 10 cm from the ileocaecal valve. Her weight reduced to 103 kg. Diarrhoea, steatorrhoea and iron-deficiency anaemia subsequently developed but these problems resolved. Two further lipectomies were performed in 1976 (apronectomy) and 1978 (right thigh reduction). Her weight was then 101 kg. In 1979, weighing 80 kg, she was admitted with chronic renal failure and Coombs-negative haemolytic anaemia. B_{12}, folate and iron stores were normal. Her urea was 13 mM/litre, creatinine 440 μM/litre and Cr^{51}-EDTA clearance

20 ml/min. The C_3 component of complement was depressed and renal biopsy showed interstitial nephritis and oxalate deposition.

In May 1980 chest radiograph showed consolidation in the posterior segment of the right upper lobe and apical segment of right lower lobe. A Mantoux test (1 in 10 000) produced 3 cm of induration. Sputum culture revealed *Mycobacterium tuberculosis* sensitive to rifampicin, ethambutol and isoniazid, and chemotherapy was commenced with these drugs.

Results

Serum levels during treatment are shown in Table I. It was found necessary to double the dose of rifampicin from 600 mg to 1200 mg to obtain adequate blood concentrations. Isoniazid in a daily dose of 300 mg and ethambutol in a dose of 1500 mg (20 mg/kg) on alternate days proved to be adequate.

Table I. Results of drug assays

Drug (target levels in brackets)	*Serum levels* (μg/ml) (time in hours after 8 a.m.)								*Dose* (given at 8 a.m.)
	0	1	2	3	4	6	8	12	
Rifampicin	0	0	0.1	0.46	0.95	1.2	0.53	0.13	600 mg
(5–10 μg/ml at 2 hr)	0	0.5	1.5	1.8	4.0	6.4			1200 mg
	0		3.7		4.7		2.5		1200 mg
Ethambutol – alternate day regimen									
(5–12 μg/ml at 2–4 hr)	1.2	4.35	7.7	7.05	6.4	4.65	3.5		1500 mg
(2 μg/ml at 24 hr)	2.7	2.0	1.95		1.65	1.65	1.35		no dose given
Isoniazid									
(3–5 μg/ml at 1–2 hr)	0.4	4.3	5.8	2.6	2.3	1.4	0.6		300 mg

No drug intolerance was noted and liver function tests, urea and electrolytes remained unchanged. Her ESR fell from 110 to 45 after 15 weeks of treatment with considerable improvement in the chest radiograph appearances. Urinary steroid excretion remained at the lower limit of normal with no precipitation of hypocortisolism, a potential risk because of the shortening of the blood half-life of cortisol while on rifampicin. Clinical and radiological progress has been satisfactory over the ensuing year's therapy. She has been unable to provide further sputum for culture.

Discussion

Jejunoileal bypass had been associated with many complications, including liver dysfunction (Maxwell et al. 1977), biliary and renal calculi, malabsorption of iron, fat and vitamins and an immune-complex syndrome of polyarthritis, erythema nodosum, skin rashes, hepatic granulomatosis, episcleritis and haemolytic anaemia (Wands et al. 1976; Pilkington 1979). The antigen source is thought to arise from overgrowth of *E. coli* and bacteroides in the bypassed segment and the syndrome may be treated by antibiotics, metronidazole in particular. Renal damage is also associated with jejunoileal bypass and is thought to be secondary to both immune-complex nephritis and oxalate nephropathy (Drenwick et al. 1978). There was evidence of such an immune-complex syndrome in our patient, namely haemolytic anaemia, renal damage and a depressed C_3 level. Tuberculosis in patients with bypass may be atypical, with negative skin tests and progressive systemic involvement (Bruce & Wise 1977) but this was not so in our patient.

The three antituberculous drugs used in our patient are thought to be absorbed in the stomach, duodenum and jejunum. We achieved adequate blood drug concentrations using a conventional dose of isoniazid, with a peak at the normal time of 1–2 hours after ingestion. The dose of ethambutol and interval between doses was modified to take account of chronic renal failure. The peak was at the normal time of 2–4 hours and on the day that no drug was given (alternate day dosage) the level was just at the therapeutic level, with subsequent minimal risk of ocular toxicity. Thus the absorption of these two drugs appears to be satisfactory after jejunoileal bypass, as has been noted elsewhere (Bruce & Wise 1977; Polk et al. 1978). Gut transit times are slowed after bypass, possibly as a result of altered gut polypeptide secretion (Pilkington 1979) and this may promote better absorption.

The situation with rifampicin is more complex, and in any patient blood concentrations may vary after single doses particularly in relation to food (Siegler et al. 1974; Mandell & Sande 1980). In man, rifampicin is converted in the liver to 25-desacetyl rifampicin which is slightly less active against *M. tuberculosis* (Mandell & Sande 1980). Both rifampicin itself and this metabolite are excreted in the bile, but unlike rifampicin, there is no enterohepatic circulation of 25-desacetylrifampicin which is thus lost in the faeces. After jejunoileal bypass decreased enterohepatic circulation of rifampicin and increased faecal loss might account for the rapid decline in blood levels found by Bruce and Wise (1977). On the other hand adequate levels of rifampicin have been reported 2½ hours post-dose after massive small-bowel resection (Wake et al. 1980). In our patient there appeared to be a malabsorption pattern with delayed and attenuated absorption. Although enzyme induction and faster breakdown occurs initially, after two weeks of treatment with 600 mg half an hour before breakfast there should be a peak level of rifampicin at 2 hours (5–10 μg/ml), decreasing to zero at 8–12 hours. In our patient the peak was delayed and drug was still detectable at 12 hours (Table I).

Acknowledgements

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PULMONARY BERYLLIOSIS: REPORT ON A FATAL CASE

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Summary

A fatal case of pulmonary berylliosis in a 59-year-old male is described. Three months after a heavy exposure to the dust of broken fluorescent light bulbs he developed severe respiratory distress with bilateral lower zone opacities on the chest radiograph. Histological examination of a lung biopsy revealed inflammatory changes with a granulomatous component and some necrosis. The diagnosis of berylliosis was confirmed by determination of beryllium in lung tissue by chemical analysis. Two years after the onset of symptoms the patient died of respiratory failure.

Introduction

Acute lung disease following exposure to beryllium was described as early as in 1933 (Weber & Engelhardt 1933) and the chronic form in 1946 (Hardy & Tabershaw 1946). The use of beryllium in the United States was minimal until World War II, but a registry of beryllium cases in Massachusetts General Hospital established in 1952, had accumulated 271 cases by 1955, nearly half of whom (46%) derived from fluorescent light bulb manufacturing (Hardy 1963). At the end of 1977 the Registry contained 887 cases (Hasan & Kazemi 1973; Spince & Kazemi 1980). Beryllium hazards, including possible carcinogenicity, were extensively reviewed in 1980 (*Environmental Research* 1980).

In 1950 guidelines for preventive measures were instituted by the Atomic Energy Commission. More than half of the known cases, however, had been exposed to beryllium after 1950, owing to its wide use in modern industry. Beryllium has now been omitted from light bulbs but is used, especially with copper, as a hardening agent in alloys which have a high tensile strength and conductivity for use in electric switches and in sparkless tools. Beryllium–nickel alloys are used in the matrix of diamond drills and in space-ships. Atomic reactors need beryllium as a moderator to retain neutrons, and finely powdered beryllium is used as an additive in rocket fuel. Normally, beryllium occurs as oxides, in complex aluminosilicates, which are widely distributed though in negligible quantities. It has never been found in plants, yet coal contains some beryllium. The normal adult human body contains traces of beryllium, of which 75% is in bone (Venugopal & Luckey 1973). No known detoxification mechanism exists in mammals for beryllium. Once in the organism beryllium and its salts are retained. Poisoning occurs from inhalation of dust and gas, and nutritional hazards are non-existent.

Beryllium is an industrial health hazard at plants of beryllium metal extraction and refining, and at nuclear reactor plants. It is also an environmental hazard in areas where coal is burnt extensively or near rocket bases. Thus in spite of safety measures new cases are constantly added to the Registry (Hasan & Kazemi 1974; Slavin 1976). The chronic form especially is also being reported from Europe (Jordan & Darke 1958; Sneddon 1958; McCallum et al. 1961; Wurm & Ruger 1962; Rees 1979).

Most cases are probably not noticed or are misdiagnosed as pneumoconioses, sarcoidoses or tuberculosis, unless the history of exposure to beryllium is immediately obvious. The radiological and histological findings may be non-specific and do not suggest the true nature of the disease unless the causative agent is suspected. Hasan and Kazemi (1974) have listed the criteria required for the diagnosis of beryllium lung disease:

1. Establishment of beryllium exposure
2. Objective evidence of lower respiratory tract disease
3. Radiologic evidence of interstitial fibronodular disease
4. Evidence of restrictive or obstructive defect
5. Pathological changes consistent with beryllium disease and presence of beryllium in lung tissue.

We present a case which fulfils these criteria. The patient was followed up from his first symptoms of acute beryllium disease until his death two years after exposure.

Case Report

The patient was a 59-year-old male owner of an electric shop. He had had well-controlled diabetes for ten years, but circulatory complications developed in 1975. Three toes were amputated, and an endarterectomy was performed to reopen two obstructed superficial femoral arteries. The results were good, but microscopic hematuria complicated the use of anticoagulants. The patient had been otherwise well, except for tuberculous pleuritis, in 1944, and for longstanding psoriasis with arthropathy.

The fatal illness

The symptoms of the fatal illness started suddenly in October 1976 with severe coughing. After three weeks of gradually increasing symptoms the patient visited the local centre for tuberculosis. The chest radiograph, which had been normal in the spring of 1976, now revealed a dense, round opacity with a diameter of 2 cm in the lateral aspect of the left lung. A metastatic neoplasm was suspected, and the patient was hospitalized. As respiratory function was severely impaired, no operation was performed, and the patient was followed till January 1977. By then the respiratory function had spontaneously improved enough to permit thoracotomy. The chest radiograph still revealed the infiltrate with possible air-fluid level.

Operation

The lesion in the dorsal part of the lingula was removed and sent for immediate frozen-section examination. The pathologist reported non-neoplastic, inflammatory changes with a granulomatous component and some necrosis. Meanwhile, another nearby mass had been detected and the entire lingula was removed. The lower lobe appeared healthy, but the upper lobe displayed numerous fine granular densities and a small mass deep in the apical segment.

Histology

In paraffin sections of the infiltrates in the lingula, severe inflammatory changes were seen (Fig. 1). The lung parenchyma was severely damaged, and both necrosis and firm fibrotic scars were observed. The cellular infiltrate consisted of lymphocytes and granulocytes, the latter often seen as small abscesses. Around small necroses, abundant histiocytes were seen together with giant cells of foreign-body type. Examination in polarized light revealed small, needle-like crystals mostly joining the abundant carbon particles. Their distribution did not correlate with the appearance of the foreign-body giant cells nor with the severity of the inflammation. Stains for tubercle bacilli and fungi were negative.

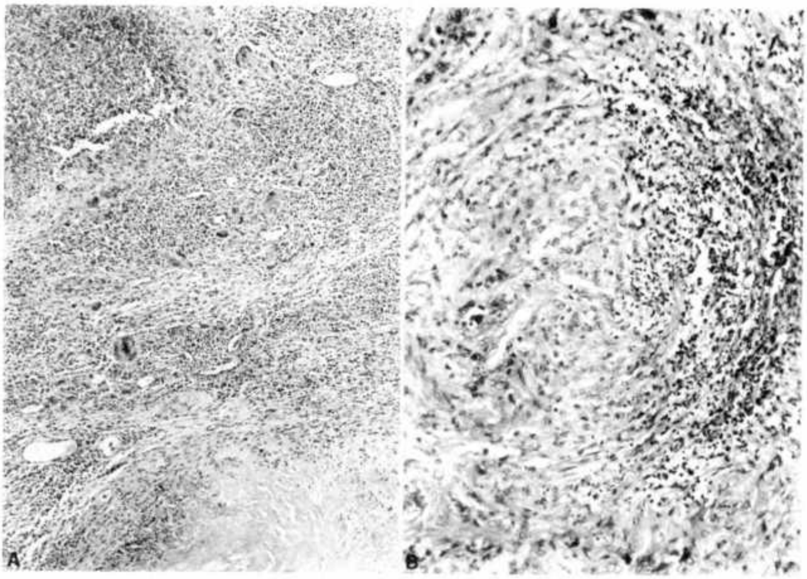

Fig. 1. Micrographs of the lesion removed in operation in January 1977. A heavy inflammation with some necrosis and foreign-body type giant cells. Hematoxylin–eosin. × 120 and 200

The pathologist concluded that the changes reflected severe inflammation with necrosis, histiocyte reaction and some foreign-body irritation without 'specific' changes. Subsequently, the possibility of berylliosis was suggested by Professor Erkki Saxén, and the tissue, still in formalin, was sent for chemical analysis.

Determination of beryllium

The analysis was performed with atomic absorption spectrometry (Perkin–Elmer, type 603). The tissue weighed 0.723 g and its beryllium content was 3.1 μg/kg (wet weight).

History of exposure

After the pathologist's diagnosis and the chemical confirmation, the patient was questioned about possible exposure to beryllium. He had owned a small electric shop for ten years, and in June–July 1976 he had had a month-long contract with a large automobile factory to change all the fluorescent bulbs in the assembly halls. Altogether, more than 1000 old bulbs were removed and replaced. The patient had personally supervised the work and had frequently participated in the removal of the bulbs. The discarded bulbs were smashed in trucks and the patient had assisted in this phase of the work. He recalled that the broken bulbs had produced a lot of dust.

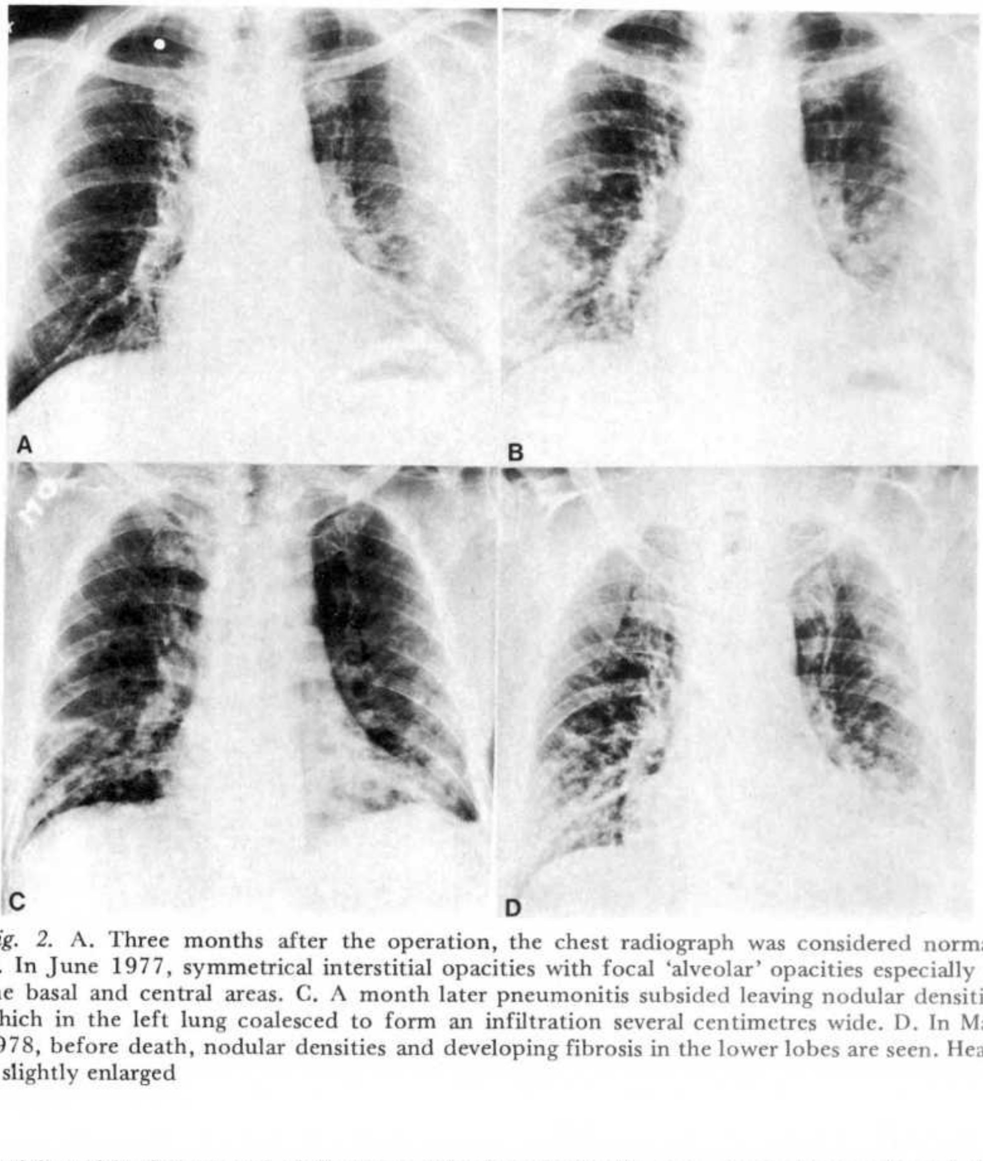

Fig. 2. A. Three months after the operation, the chest radiograph was considered normal. B. In June 1977, symmetrical interstitial opacities with focal 'alveolar' opacities especially in the basal and central areas. C. A month later pneumonitis subsided leaving nodular densities which in the left lung coalesced to form an infiltration several centimetres wide. D. In May 1978, before death, nodular densities and developing fibrosis in the lower lobes are seen. Heart is slightly enlarged

Further analysis revealed that the bulbs were installed in 1960–1 and, according to their manufacturer, beryllium was at that time still used for coating the inner surface of the bulbs.

Progress

While the diagnosis of beryllium lung disease was being confirmed the patient received antituberculosis therapy. He was admitted to hospital again three months after the operation because of shortness of breath and general weakness. Pneumonia and microscopic haematuria were diagnosed as well as poor control of his diabetes. The antituberculosis treatment was discontinued, the diabetes was controlled and antibiotics were given. Some coughing and breathlessness persisted, but his condition improved, and the chest radiograph was considered to be normal (Fig. 2A).

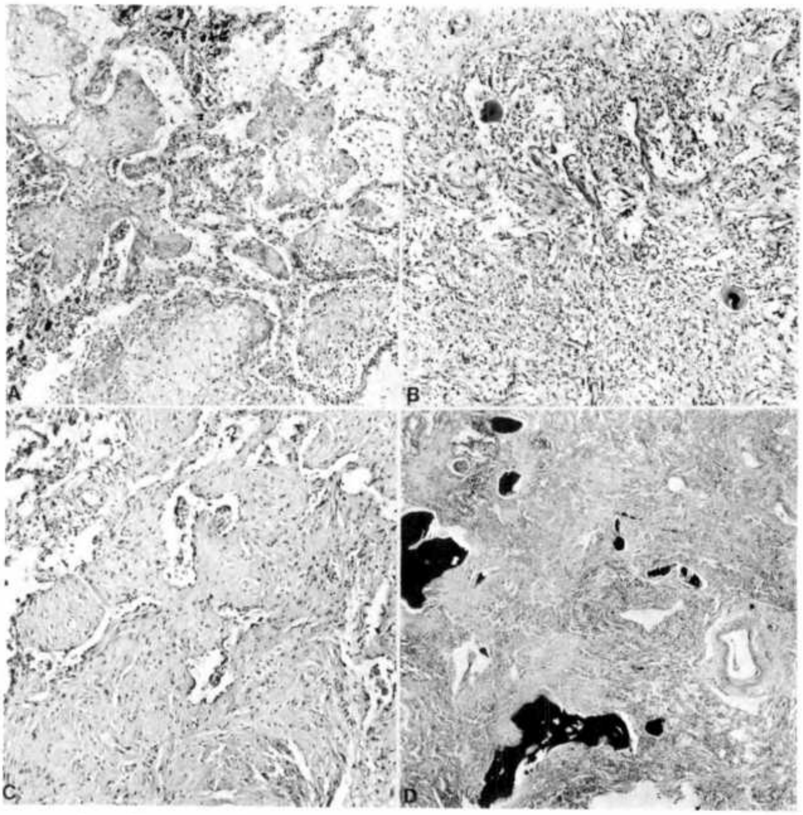

Fig. 3. Micrographs of lung specimens taken at autopsy two years after exposure to beryllium. Hematoxylin–eosin. A. Alveolar histiocytosis, infiltration of inflammatory cells in the interstitial tissue and some foreign material. × 120. B. Typical changes of a chronic, fibrotizing inflammation with some Schaumann bodies. × 120. C. An area of dense, fibrous scars. × 120. D. Changes reflecting a chronic, fibrotizing inflammation with osseous metaplasia. × 60

In June 1977, blood was first seen in the sputum, and the patient developed a fever. On admission, he was breathless and anorectic; he coughed heavily, and rales were heard on both sides. The chest radiograph now showed symmetrical opacities with additional 'spotty' infiltration in the lower zones (Fig. 2B). During antibiotic treatment, the pneumonic infiltrations disappeared, but the nodular changes remained unaltered (Fig. 2C). In September, the patient again developed an acute respiratory illness with fatigue, weakness and microcytic, hypochronic anaemia. Serum creatinine and blood sedimentation rate were both elevated.

In March 1978, the left leg was amputated because of severe ischaemia. The patient was in poor condition during the operation with poor control of diabetes. Pulmonary oedema complicated the operation. He recovered well, but the sedimentation rate remained over 100 mm per hour, serum creatinine was elevated and microscopic haematuria persisted. Dyspnoea, cough, fatigue and pain in the chest continued.

Two months later these symptoms brought him back to the ward. Fatigue was extreme and shortness of breath occurred on the slightest effort. There was no evidence of infection, and no elevation of temperature; there was blood but no pathogen in the sputum. The blood pressure was low, the pulse rapid; and there was no oedema. The haemoglobin value was low, creatinine had risen, microscopic haematuria persisted and cardiac insufficiency with pulmonary oedema developed. The chest radiograph on this admission (Fig. 2D) showed increasing lower zone fibrosis and cardiac enlargement. Corticosteroid treatment was planned, but the patient died before its onset.

Autopsy findings

The lungs were adherent and covered with fibrin. Pulmonary oedema was present, and in the basal parts of both lungs numerous small dense nodules with frequent calcification were seen. The heart showed moderate hypertrophy and sclerosis of the coronary arteries. The liver was enlarged and abnormally dark, and the spleen was large. The kidneys were large, oedematous and pale with spotty discoloration.

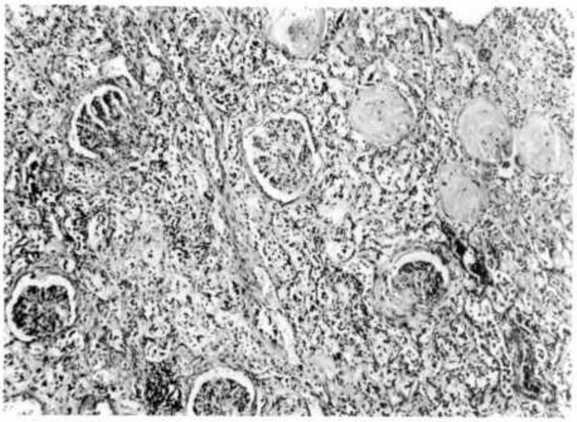

Fig. 4. A micrograph of the kidney specimen taken at autopsy. Changes typical of chronic glomerulonephritis. × 150

Microscopy

Samples were taken from different lobes of the lungs. The pathological findings showed great variation, and some unaffected areas were seen. The commonest change was alveolar histiocytosis and exudate with inflammatory infiltrate in the interstitial tissue (Fig. 3A). In one of the samples, a small area of necrosis surrounded by neutrophils and some histiocytes was seen, reflecting an active inflammatory process accompanied by Schaumann bodies (Fig. 3B). In addition, dense fibrotic scars were detected (Fig. 3C). A most distinct finding was ossification in many places; small ossifying pieces were seen in the lung parenchyma , frequently associated with active inflammation and fibrosis (Fig. 3D). Microscopical examination of the kidney revealed changes typical of chronic glomerulonephritis with severe glomerular lesions (Fig. 4). Features typical of diabetic kidney disease were not observed nor those suggesting a generalized arteritis.

Chemical determinations

Tissue samples for beryllium determination were taken from both lower lobes of the lung and from the liver. Macroscopically abnormal areas were chosen. As the manufacturer recalled that mercury had been used in the production of the bulbs together with beryllium, Hg was also determined.

Beryllium was again determined by atomic absorption spectrometry, using the Perkin–Elmer model 603 apparatus, and mercury by Perkin–Elmer Coleman MAS-50 mercury analyser according to Kivalo et al. (1974). The results are given as μg/kg wet weight (Table I).

Table I. Content of beryllium and mercury in three tissue samples

	Beryllium (μg/kg wet weight)	*Mercury* (μg/kg wet weight)	*Ratio*
Lung: right lobe	3.4	12	0.29
Lung: left lobe	14	39	0.28
Liver	25	76	0.30

Comment

The case represents fatal lung disease associated with exposure to beryllium. All the criteria listed in the introduction are met, and both the histological and radiographic findings were compatible with those reported in pulmonary beryllium disease (Wilson 1948; Spencer 1963; Weber et al. 1965; Zeck & Cugell 1977). The beryllium content of the lungs was elevated with levels up to ten times those quoted in the literature for non-diseased lungs (Hasan & Kazemi 1974). The course of the disease was, however, somewhat exceptional with an acute phase developing rapidly into a subacute, severe condition. Due to a block in communication the clinician was not aware of the proper diagnosis before the second, fatal phase of the disease and hence, corticosteroid therapy, known to be beneficial in this disease (Zeck & Cugell 1977) was not given.

The role of the inhaled mercury remains uncertain. According to the manufacturer, the surface of the bulbs was coated with a beryllium–mercury amalgam, and both these components were traced in the diseased tissues. It is noteworthy that the ratio of these two was almost constant in the three samples, a finding consistent with the idea of their common origin.

The pathogenesis of beryllium lung disease is not known. Both a direct toxic effect (Hardy 1965; Browne 1966) and a hypersensitivity mechanism (Alridge et al. 1949; Sneddon 1958) have been suggested. The varying sensitivity to beryllium seems to favour the immunological theory (Kazantzis 1978). In our case, the course of the disease with a severe, necrotizing process of acute onset two months after exposure may also favour the allergic theory.

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MICROSCOPIC TUMOUR EMBOLI FROM CARCINOMA OF THE PROSTATE

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Summary

A case of pulmonary tumour microemboli from an unusual site, the prostate, is presented. A comparison is made with previously described cases of tumour microemboli.

Introduction

Although as many as 50% of autopsies for prostatic carcinoma show evidence of lung metastases (Varkarakis et al. 1974) these rarely present a clinical problem. Pulmonary hypertension and cor pulmonale are unusual sequelae of pulmonary metastases but may rarely result from tumour microemboli (Brill & Robertson 1937). The commonest sources of tumour emboli are carcinoma of the breast, stomach, large bowel or cervix, primary hepatoma or choriocarcinoma (Kane et al. 1975). We describe a case in which prostatic tumour microemboli resulted in an unusual presentation of this common carcinoma with pulmonary hypertension.

Case Report

A 66-year-old retired sewerage pump operator with a nine-year history of reversible obstructive lung disease and eosinophilia developed pain in the left hip in June 1980. Four months later he developed acute dyspnoea which increased in the two weeks before admission, by which time he was severely breathless at rest. On examination he was acutely ill, centrally cyanosed and wasted. A third heart sound was audible at the left sternal edge. There were no abnormal signs on auscultation of his lungs. Rectal examination revealed a large, hard prostate.

Chest radiograph showed no cardiac enlargement and clear lung fields. Lumbar spine and pelvic radiographs showed patchy sclerotic changes in the bones. Arterial blood gases breathing air were: PaO_2 6.86 kPa (51.8 mm Hg), $PaCO_2$ 3.17 kPa (23.9 mm Hg), hydrogen ion 33.1 nmol/litre (pH 7.48). Spirometry showed FEV_1 2.5 litres, FVC 4.2 litres, compared to values of FEV_1 1.65 litres, FVC 3.4 litres in 1974 (predicted values: FEV_1 2.75 litres, FVC 3.86 litres). Technetium-99^m perfusion lung scan showed multiple bilateral peripheral perfusion defects. Alkaline phosphatase was 500 i.u./litre (normal < 95 i.e./litre) and acid phosphatase was 24.4 i.u./litre (normal < 3.5 i.u./litre). ECG showed an axis of + 90°, but there were no other significant abnormalities, in particular no evidence of right ventricular strain.

Despite anticoagulation and oxygen therapy he remained severely dyspnoeic. Four days after admission he deteriorated suddenly with left pleuritic pain, hypotension and elevated jugular venous pressure. He died later that day.

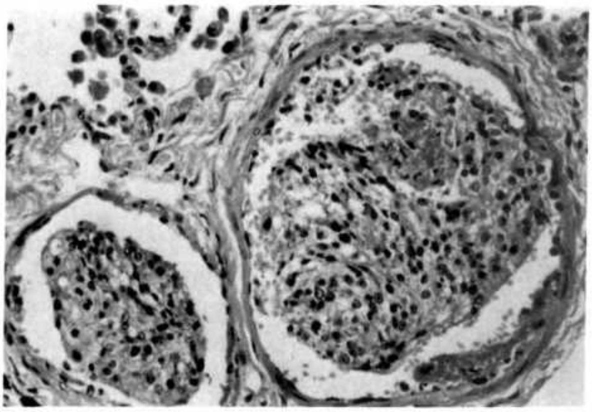

Fig. 1. Tumour emboli within pulmonary arterioles. Haematoxylin and eosin × 200

Autopsy Findings

The prostate was moderately enlarged with firm nodules throughout. Pelvic veins were free from thrombus. The heart was enlarged due to left but not right venticular hypertrophy. There was no evidence of pulmonary infarction and no emboli in the major divisions of the pulmonary artery. Apart from a few small (up to 0.5 cm diameter) scattered red nodules, the lungs appeared macroscopically normal. Metastases were present in the vertebrae and in the para-aortic lymph nodes.

Histology confirmed carcinoma of the prostate. In the lungs the major changes were in the small arteries and arterioles. 27% contained clumps of tumour cells (Fig. 1). In a further 17% the lumen was occluded, or severely obstructed by a proliferation of loose intimal fibrous tissue (Fig. 2). Another 7% showed recent thrombus and in 2% thrombus and tumour cells were present. The changes were present in all parts of the lungs.

Discussion

Kane et al. (1975) reviewed 1085 autopsies of solid malignant tumours and found 26 (2.4%) with microscopic tumour emboli, only nine of whom had dyspnoea. Unusually, four of the cases had emboli originating from prostatic neoplasms, a

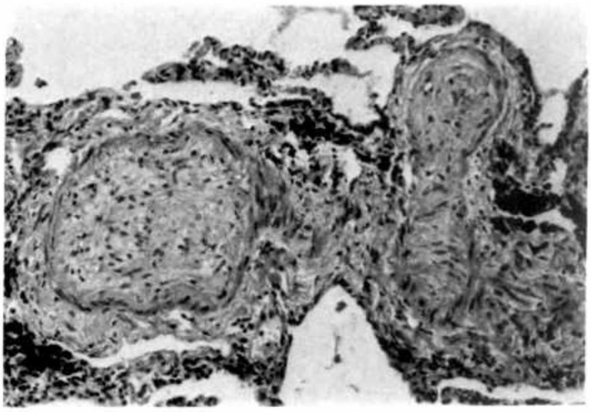

Fig. 2. Small pulmonary arteries occluded by proliferated intimal tissue. Haematoxylin and eosin × 125

source not previously described in English. The case we describe demonstrates many features of microemboli to the lungs from malignant neoplasms (Brill & Robertson 1937). He had severe dyspnoea and hypoxaemia but paradoxically the chest radiograph was normal and spirometry was well preserved. The appearance of the lung perfusion scan with multiple peripheral perfusion defects was similar to that described for other tumour microemboli but interpretation was complicated by the history of reversible air-flow obstruction. The antemortem diagnosis was multiple thromboemboli, a common error when tumour emboli are responsible (Kane et al. 1975, Gelfand & Tesler 1962). Unlike most previously described cases, our patient had little clinical or electrocardiographic evidence of cor pulmonale, which suggests that emboli had occurred over several weeks.

Intimal thickening in the large pulmonary arteries and in the muscular arteries, particularly those of the upper lobes is a normal ageing process. It is also a feature of chronic primary or secondary pulmonary hypertension, when it is associated with generalized medial hypertrophy. The intimal proliferation occurred in both upper and lower lobes and was so marked in some vessels as to occlude the lumen (Fig. 2). Since it was so marked and was in excess of any change in the medial thickness it seems unlikely that it represents a reaction to pulmonary hypertension. It has been suggested that intimal proliferation is a response to the presence in the lumen of tumour cells themselves (Morgan 1949; Storstein 1951), but it would seem more likely that it results from organization of thrombus secondary to arterial occlusion by tumour emboli. In our case, although only a few recent thrombi were present, they did occur in all sections examined. Kane et al (1975) described two cases of prostatic microemboli with intimal thickening of 1.2% of arteries, and both cases had had unexplained dyspnoea, while two other cases did not show significant intimal thickening and had no dyspnoea.

Thromboemboli to the lungs are rarely a feature of prostatic carcinoma and possibly some cases are misdiagnosed as thromboemboli, since the four previously described cases were found in a retrospective study of a large series of autopsies (Kane et al. 1975). In patients with distressing and unrelieved dyspnoea, antitumour treatment may offer better relief than anticoagulation.

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Short Communication

SEVERE ACUTE ASTHMA – A PROBLEM PATIENT

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Summary

A patient with severe acute episodic asthma is described who has required artificial ventilation as a life-saving procedure on 20 occasions. To obtain easy access to her circulation during attacks, an arteriovenous fistula has been fashioned in her thigh and has been found to be of considerable value.

Introduction

In 1968 the Respiratory Unit at this hospital introduced a service to allow direct admission of patients with severe acute asthma (Crompton & Grant 1975). We report the problems encountered with the treatment of a young woman frequently admitted to hospital through this service.

Case Report

The patient who has a family history of asthma and is atopic on routine skin testing is now aged 22. She developed eczema at three months and had her first attack of wheeze at the age of six. Her asthmatic attacks became more frequent and were not controlled with regular inhalations of salbutamol and sodium cromoglycate. By the age of 11 she was having frequent episodes of asthma despite maintenance oral prednisolone therapy.

In the last eight years she has had 47 emergency admissions with acute severe asthma and required tracheal intubation and mechanical ventilation as a life-saving procedure on 20 occasions. The main indication for ventilation during each attack was extreme respiratory distress. On 13 occasions she has developed significant carbon dioxide retention (mean arterial $P\text{CO}_2$ 9.04 kPa, range 6.9–13.2 kPa) with corresponding respiratory acidosis (mean arterial hydrogen ion concentration 64 nmol/litre, range 52–91 nmol/litre) prior to intubation. Most attacks evolved at alarming speed with severe asthma developing in a matter of minutes. Despite urgent direct admission to the Unit she has usually arrived *in extremis* and had a respiratory arrest on one occasion.

Fortunately, she has usually responded promptly to resuscitative treatment. In 1977, for example, she was unconscious on arrival at the Unit and her arterial $P\text{CO}_2$ was 9 kPa (68 mm Hg). She was ventilated overnight and discharged the following day after recording pulmonary function tests within her predicted normal range. Between episodes of asthma she has been virtually symptom-free and has been able to lead a normal life.

In 1977 it became evident that resuscitation was being delayed by difficulty in gaining access to her circulation because all her superficial veins had become obliterated as a result of repeated cannulation. In order to facilitate both arterial blood sampling and the intravenous administration of fluid and drugs, a GORE-TEX arteriovenous fistula was fashioned between her right femoral artery and vein. Since this operation, she has had 14 emergency admissions with asthma and required artificial ventilation on seven occasions. The fistula, which has now been punctured on at least 65 occasions, has proved an invaluable asset, providing easy access to her circulation.

Discussion

It is perhaps remarkable that this patient is still alive and leading a normal life. The fact that she could admit herself urgently (usually in less than 30 minutes) to a Respiratory Unit has obviously been vital to her survival. Unfortunately, it has so far been impossible to suppress her asthmatic attacks with maintenance oral prednisolone or ACTH therapy and there are no obvious factors which appear to 'trigger' her asthma.

In the last seven years during which time this patient has required ventilation 20 times there have been only seven other occasions when an asthmatic patient has been ventilated in our Unit. The frequency with which this patient has been ventilated reflects the severity of her asthmatic attacks rather than our policy in the treatment of severe acute asthma. Her pattern of repeated severe asthmatic attacks is not recognized in two recent reports of the problems of asthmatic patients who require ventilation (Webb et al. 1979; Westerman et al. 1979).

Vascular access grafts have proved useful in the administration of intravenous cytotoxic agents in cancer patients (Raaf 1979), blood products in haemophiliacs (Goldenberg et al. 1980), parenteral nutrition in patients with severe malabsorption (Baird et al. 1980), and even insulin in a patient with recurrent diabetic ketoacidosis (Guba et al. 1979).

The insertion of an artificial arteriovenous fistula in our patient has made intravenous therapy and arterial blood sampling easy but has necessitated long-term anticoagulant therapy to maintain its patency. We would recommend that this measure be considered in the few patients who have frequent life-threatening attacks of asthma where access to the circulation is difficult.

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Short Communication

PLEURAL MESOTHELIOMA: DIAGNOSIS BY TREPHINE BIOPSY

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Summary

Fourteen patients submitted to trephine biopsy of the pleura at the London Chest Hospital for suspected mesothelioma were reviewed. A diagnosis was made in twelve patients including nine with mesothelioma. In seven of these patients other percutaneous aspiration techniques had been unsuccessful. No complications were encountered, and no instance of needle track spread was recorded.

Introduction

In a recent review of patients with malignant pleural mesothelioma, it was stated that diagnosis proved difficult to establish unless open biopsy was performed (Law et al. 1981). In addition the tendency of the tumour to track along previous aspiration sites and surgical incisions was recognized. These comments prompted us to look at the records of those patients at the London Chest Hospital in whom trephine biopsy of the pleura (Steel & Winstanely 1969) was performed for suspected mesothelioma.

Methods

In a retrospective study, the case notes, radiographs and, when available, postmortem reports of 14 patients at the London Chest Hospital in whom a clinical diagnosis of mesothelioma was suspected and who were submitted to trephine biopsy of the pleura were reviewed. Follow-up notes were obtained from other hospitals and chest clinics in those instances where the patient had been referred to the London Chest Hospital for diagnosis only. Previous attempts at pleural aspiration and Abram's needle biopsy were noted and any post trephine biopsy complications including chest wall metastases recorded.

Results

Of the 14 patients, 12 were male, and two were female. Ages varied from 42 to 76 years with a mean of 60.9 years. A history of occupational asbestos exposure was obtained in 13 cases. Pleural effusions had been present in seven patients.

Tissue for histological examination was obtained in 12 patients. Mesothelioma was diagnosed in nine, probable adenocarcinoma in two and fibrous thickening in one (see Table I). No specimen was obtained from two patients.

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Six of the nine patients with mesothelioma and one of the two with probable adenocarcinoma had undergone previous unsuccessful attempts at pleural aspiration and Abram's needle biopsy.

Unfortunately only six of the nine patients in whom mesothelioma had been diagnosed and who subsequently died underwent postmortem examination, but in five (83%) the diagnosis was confirmed and accepted by the Pneumoconiosis Medical Panel; in the sixth the Panel's diagnosis was rhabdomyosarcoma.

Complications

No immediate complications occurred following trephine biopsy. Routine post biopsy chest radiographs excluded pneumothorax. A single chest wall metastasis was recorded but this was distant from the biopsy site.

Table I. Results of trephine biopsy of pleura

Biopsy diagnosis	*No. of patients biopsied*	*No. of postmortem examinations*	*Postmortem confirmation of biopsy histology*	*Postmortem diagnosis of mesothelioma*
Mesothelioma	9	6	5	5
Probable adenocarcinoma	2	2	2	0
Fibrous thickening	1	1	0	1
No specimen	2	1	—	1
Total	14	10	7	7

Discussion

Aisner and Wiernik (1974) commented that the incidence of mesothelioma is increasing and that it is no longer considered a rarity. Although at present there is no effective treatment, this does not detract from the importance of differentiating it from potentially treatable conditions.

There is a general impression that nothing short of open biopsy is of any value in establishing the diagnosis of mesothelioma. Caravelli and Zaman (1978) maintain that although percutaneous aspiration techniques may help confirm the suspicion of malignancy, there is still the need for thoracotomy to establish the definite diagnosis. Elmes and Simpson (1976) stress the difficulty in achieving a positive histological diagnosis unless a large volume of tissue is available for examination. In cases where needle biopsy and cytology were unhelpful or where no free fluid was present, open biopsy was often performed in their patients. They found that cytological examination of fluid proved correct in 7 of 142 cases (4%), and needle biopsy in 18 of 69 cases (26%), but even when open biopsy was performed the diagnosis was made in only 45 of 115 cases (38%). On the other hand Edge and Choudhury (1978) obtained an acceptable diagnosis by pleural biopsy in 30 of a total of 50 patients using both trephine and Abram's needle techniques. Our numbers are small but they suggest the accuracy of trephine pleural biopsy. This is underlined by mesothelioma having been successfully diagnosed in six patients and adenocarcinoma in one patient after other percutaneous techniques had failed.

An additional advantage is that trephine biopsy may be performed in the absence of free pleural fluid.

Thoracotomy scar metastases may occur and needle track tumour is a recognized risk (Law et al. 1981). Elmes and Simpson (1976) commented on tumour masses recorded in the notes of 35 of a total of 267 patients and 80% of these were related to needle biopsy or thoracotomy scars. It is encouraging that track spread was not recorded following our 14 trephine biopsies, although it must be taken into consideration that seven patients had also undergone other percutaneous needle biopsies. Track spread may possibly not have been recorded in the follow-up notes but this would be surprising as metastases are usually painful, as Elmes pointed out. It seems possible that the trephine technique might avoid subcutaneous deposits by containing the core of biopsy material within a revolving metal cylinder in contrast to Abram's biopsy where malignant tissue is dragged through the wound.

A larger series may confirm the impression that pleural trephine biopsy is safer than open or Abram's needle biopsy and of comparable accuracy with thoracotomy in the diagnosis of malignant pleural mesothelioma.

Acknowledgements

Our thanks are due to Dr D. R. Winstanley and Professor B. E. Heard for interpretation of the histology and to Dr W. R. Parkes for communicating the findings of the Pneumoconiosis Panel.

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Short Communication

LEFT VOCAL CORD PARALYSIS AND CHRONIC OBSTRUCTIVE AIRWAYS DISEASE

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Summary

We describe a case of left vocal cord paralysis secondary to pulmonary artery dilatation in a patient with chronic bronchitis and emphysema.

Introduction

Left vocal cord paralysis is a well recognized but rare complication of dilatation of the pulmonary artery, usually secondary to mitral stenosis (Thomson & Kistin 1948). We report a case of left recurrent laryngeal nerve paralysis associated with pulmonary artery dilatation secondary to chronic bronchitis and emphysema.

Case Report

A 48-year-old butcher presented to the clinic with sudden onset of hoarseness and was found to have left vocal cord paralysis. He had suffered from asthma as a youth but this had cleared in adolescence. He was a heavy smoker and had a long history of a chronic productive cough and breathlessness especially on hills and stairs. His only drug treatment was orciprenaline syrup. On examination he was plethoric and had central and peripheral cyanosis. Blood pressure was 140/90 mm Hg. The jugular venous pressure was not elevated. There was a right ventricular heave, a loud pulmonary second sound and a fourth heart sound. Breath sounds were harsh with widespread inspiratory and expiratory rhonchi. Liver and spleen were not palpable and there was no peripheral oedema.

His haemoglobin was 22 g/dl with a haematocrit of 68%. Platelets and the white cell series were normal. Chest radiograph revealed a large heart with prominence of the main pulmonary artery and its proximal branches. The electrocardiogram showed P pulmonale, right axis deviation and right ventricular hypertrophy. His PaO_2 was 7.1 kPa (53 mm Hg) at rest and fell on mild exercise to 5.6 kPa (42 mm Hg), and $PaCO_2$ was chronically elevated above 6 kPa (45 mm Hg). Pulmonary function tests showed a fixed obstructive pattern with FEV_1 of 1.41 litres (predicted 3.35 litres) and a low carbon monoxide transfer factor. Bronchoscopy confirmed the vocal cord paralysis but was otherwise normal. Right heart catheterization showed a raised mean pulmonary artery pressure of 42/21 mm Hg with a normal wedge pressure of 11 mm Hg. There was aneurysmal dilatation of the main pulmonary artery with dilated right and left main pulmonary arteries on pulmonary angiography (Fig. 1). Upper mediastinal tomography showed no glandular enlargement. His polycythaemia was treated with venesection and he was encouraged to give up smoking. This has resulted in some subjective improvement in his exercise tolerance. His hoarseness has only slightly improved and the radiograph has not changed during one year of observation.

Discussion

Vocal cord paralysis when associated with chest disease is usually secondary to involvement of the recurrent laryngeal nerve with bronchial neoplasm or with the mediastinal scarring of healing tuberculosis (Titche 1976). Investigations have made these highly unlikely in our patient and there is no evidence of malignancy after one year. Review of his chest radiographs taken over the last 15 years has shown a slowly enlarging heart and pulmonary arteries, associated with a deterioration in his pulmonary function. Catheter studies confirmed that his pulmonary hypertension was secondary to intrinsic lung disease and angiography revealed aneurysmal dilatation of his pulmonary artery with no evidence of pulmonary thromboembolism.

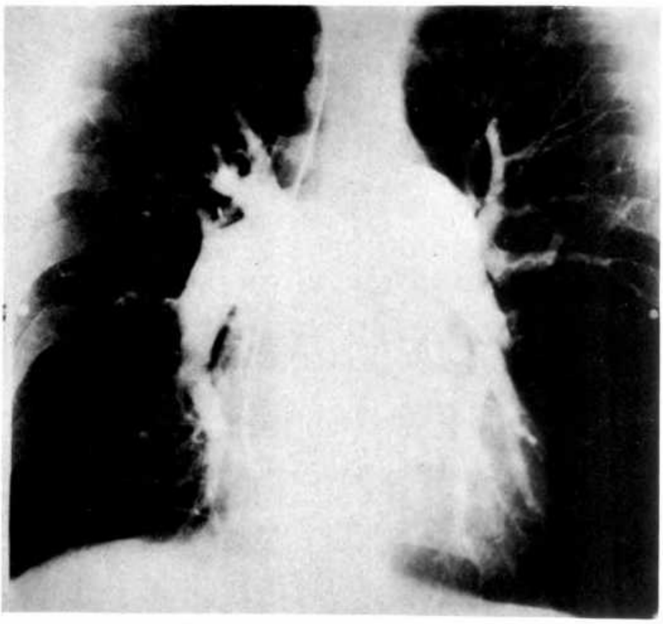

Fig. 1. Pulmonary angiogram.

Ortner in 1897 described the association between mitral stenosis and left vocal cord paralysis. He attributed this to a direct pressure effect of an enlarged left atrium on the left recurrent laryngeal nerve. However, Fetterolf and Norris in 1911 in postmortem studies showed that even a grossly enlarged left atrium cannot impinge directly onto the nerve. They maintained that the nerve was damaged by being squeezed between the dilated left main pulmonary artery and the aorta or aortic ligament. Other studies have since confirmed this mechanism (Thomson & Kistin 1948). Since that time, left vocal cord paralysis has been described in other conditions where pulmonary artery dilatation has been a feature, such as primary pulmonary hypertension, atrial septal defect and cardiac decompensation (Stocker & Enterline 1958). Pulmonary artery pressures two to three times normal as in our case seem to be a common finding in these patients (Titche 1976). Recovery of vocal cord function has not been described.

Hoarseness is an unusual complication of chronic obstructive airways disease. The above case described a previously unrecorded association between left vocal cord paralysis and pulmonary artery dilatation secondary to chronic chest disease.

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FUTURE MEETINGS OF THE BRITISH THORACIC SOCIETY

The list below gives details of future meetings, both arranged and provisionally planned. I hope this will prevent the clashing of dates with meetings arranged by other Societies.

27 and 28 January 1983	Kensington Town Hall, London. Abstracts for consideration to be submitted by 16 October 1982 to 30 Britten Street, London SW3 6NN
27–29 June 1983	Annual General Meeting, Churchill College, Cambridge

Further details of these meetings can be obtained from Dr I. A. Campbell, Sully Hospital, Sully, Penarth, Glamorgan CF6 2YA.

BRITISH THORACIC SOCIETY

On 30 June 1982 the British Thoracic Association and the Thoracic Society will merge to form a new British Thoracic Society and for three years all members of the British Thoracic Society will receive both *Thorax* and *British Journal of Diseases of the Chest.*

BOOK REVIEWS

Diagnostic Bronchoscopy
Peter Stradling
Edinburgh, London, Melbourne and New York: Churchill Livingstone. 1981, 4th edition. Pp. 159. Price £30

To describe this book as a monumental achievement is no exaggeration. The superb quality of the 190 coloured illustrations and the clarity of the explanatory diagrams and commentaries are a unique testimony to the skill of a man who is more familiar with normal and abnormal bronchoscopic appearances than perhaps anyone else in the world. Dr Stradling has exploited to the full the expertise of his technical assistants, his artist and his publishers to produce a volume which every pulmonary physician and surgeon who intends to practise bronchoscopy, and many who are already doing so, should study from cover to cover.

Inevitably, the chapters on the technique of rigid and fibreoptic bronchoscopy raise the vexed question of the advantages and disadvantages of the two methods. Dr Stradling sets these out very fairly in Chapter 3, and I doubt if any bronchoscopist competent in the use of both instruments would dispute his conclusion that the two are complementary: the disadvantages of one reflect the advantages of the other. Unfortunately, the opportunities for training in rigid bronchoscopy are steadily diminishing, mainly because the services of skilled anaesthetists for this procedure are no longer readily available. Many operators who are incapable of using a rigid bronchoscope rationalize their inadequacy in this respect by claiming that the flexible instrument has now completely superseded the rigid bronchoscope. Dr Stradling has observed that in certain critical situations, which are happily few, this may be a dangerous philosophy, but with rigid bronchoscopy rapidly becoming a lost art, it is one which respiratory medicine in general, and a few unfortunate patients in particular, may soon be forced to accept.

Because of the technical limitations to the photography of fibreoptic images, specially adapted rigid bronchoscopic equipment has had to be used to produce all the coloured illustrations in Dr Stradling's book, but these illustrations will be just as helpful to the novice fibreoptic bronchoscopist as they have been in the past to aspiring rigid bronchoscopists.

It is difficult to believe that anyone but Dr Stradling will ever be able to collect, and to photograph with such beauty and clarity, the almost infinite variety of bronchial normality and abnormality displayed in this book. We must hope it has not reached its last edition, but even should that be so, Stradling's *Diagnostic Bronchoscopy* is certain to remain an indispensable *vademecum* which trainee bronchoscopists of both technical persuasions will study avidly for many years to come.

Ian W. B. Grant

Clinical Oncology Monographs: Small Cell Lung Cancer
Eds F. Anthony Greco, Robert K. Oldham and Paul A. Bunn, Jr.
New York: Grune & Stratton Inc. 1981. 1st edition. Pp. xii + 463. Price $39.50

In recent years books on lung cancer have become one of the growth products of the medical publishing industry. Advances in the management of non-small-cell carcinomas have been negligible in terms of impact on the disease and few differences are noted between successive volumes. Happily, the converse is true for small-cell lung cancer. Major advances in management are beginning to be reflected in long-term survival. Results of large clinical trials are demonstrating a continuing improvement and emphasis on new therapeutic questions — the current major one being the role of radiation therapy in the management of limited stage disease.

This book which is devoted to small-cell lung cancer already suffers from some outdated therapeutic results but none the less is a valuable addition to the subject. Both the editors and many of the chapter authors have made major personal contributions to their chosen subjects and this is well reflected in the authority of the contents.

The chapters on therapeutic aspects which form less than half the book are valuable summaries of the state of the art and science. Even more valuable however are the sections devoted to various aspects of the biology of the disease. These subjects, which have been less frequently and often less well reviewed previously, include authors' excellent personal accounts of xenografts, in vitro characteristics and in vitro cloning, growth kinetics, hormonal production and morphological changes following therapy.

The book is well produced, easy to read and usefully referenced without being overwhelming in content. This reviewer enjoyed reading it and looks forward to a second edition in a very few years time which undoubtedly will have much new to say on these topics.

Norman M. Bleehen

Methods in Clinical Pharmacology 2: Respiratory System
Eds J. B. L. Howell & A. E. Tattersfield
London: The Macmillan Press. 1981. 1st edition. Pp. vi + 94. Price £15.50

Methods in Clinical Pharmacology 2: Respiratory System is a collection of articles first printed in the British Journal of Clinical Pharmacology, reviewing the experimental methods used in respiratory medicine.

Over the last few years there have been considerable advances in the detailed knowledge of pulmonary function and this with improved precision and simple techniques has enabled the quantitative assessment of drug action to be measured more easily. However, as the editors point out, the results of many such studies have led to conflicting results and a loss of confidence in many of the papers published. The reasons for the conflicting results are many and include lack of critical evaluation of equipment, poor understanding of the problems related to so called 'sensitive' tests of airflow obstruction without consideration of the reproducibility of the tests, and using inappropriate measurements.

The editors have imposed a strict control over the authors, who are all experts in aspects of respiratory function testing, demanding from them an explanation for the conflicting results seen in the literature, and how such problems can be avoided.

The initial part of the book deals mainly with lung mechanics and looks at static lung volumes, airway calibre assessment by the forced expiratory manoeuvre and airways resistance measurements. In each of these chapters the authors have outlined the various techniques available, the discrepancies expected by these various techniques, the factors affecting the results and normal values with the reproducibility of each measurement clearly stressed. The failure of such tests to distinguish different pathological mechanisms is also stressed. A chapter on bronchial provocation tests completes this part of the book, and here the author answers a series of self imposed questions as to the aim of such tests, the methods of provocation available and finally the interpretation of the results.

The next section of the book deals with measurement of ventilation, the assessment of control of breathing and arterial blood gas tensions and pH. A similar format is maintained for these chapters, and the techniques used here are integrated in the chapter on exercise testing. The final chapters of this exemplary short book deal with nasal resistance and the muco-ciliary clearance.

The text throughout is remarkably readable especially in view of the large quantity of information which is contained in each chapter. The use of sub-headings and sub-sections allows easier retention of this information which is only spoilt by the use of full author named references, which in places are so extensive as to lose the meaning of the sentence. However, the bibliography, although obstructive in the text is excellent, not only being up to date but is also extensive, containing many of the original references which describe the techniques discussed. The text is supported by clear, relevant figures and tables, and the book is generally well produced with clear print.

Respiratory physiologists are well served by textbooks on the experimental methods available to them, but I feel this book should be read by all research registrars in pharmacoloty or respiratory medicine who use respiratory function tests in their studies. The book is an excellent review, not only of the techniques, but outlines the errors and pitfalls in respiratory drug pharmacology.

G. M. Cochrane

Thoracic Medicine
Peter Emerson
London: Butterworth. 1981. 1st edition.
Pp. xx + 1015. Price £35

The structure of this book, as the editor indicates in his preface, is based on the premise that 'almost invariably the physician has a straight. PA chest radiograph of the patient in front of him as he starts to interrogate the patient'. Descriptions of disease are grouped together according to the gross radiological features known to the physician in the first instance. Thus there are sections describing disorders of the lung characterized by a localized abnormality and disorders characterized by a diffuse abnormal appearance on the chest radiograph. The fact that the premise is not universally applicable and that some descriptions in other sections may be associated with local or diffuse abnormality does not detract from the imaginative concept of the presentation though occasionally it results in some overlap. It should also be understood that in the descriptions of the disorders the authors do not overemphasize the importance of the chest radiograph. The first three sections are devoted to anatomy and physiology, diagnostic methods and therapeutics. All these sections are covered clearly and comprehensively, those on radiological techniques, diagnostic nuclear medicine techniques and bronchoscopy and biopsy techniques being particularly valuable.

This is an excellent textbook. It is beautifully printed and the reproduction of chest radiographs and illustrations is extremely good. It has a good index and there are remarkably few misprints in its thousand pages.

One of its merits is that in addition to valuable descriptions of disease there are accounts of great practical value throughout the text — detailed advice on contact tracing in tuberculosis, serum levels of antibiotics, the investigation of recurrent pneumonias are but few examples. The numerous tables dealing with subjects such as the adult respiratory distress syndrome, the causes of different radiographic abnormalities, the types of opportunist bacterial and fungal infection and so on will be of considerable value to clinicians faced with difficult problems and to teachers wishing to ensure that their material is soundly based.

One or two very minor criticisms are offered. This reviewer believes that the space allocated to industrial lung diseases (the same number of pages as hydatid disease) is insufficient in relation to the importance of these diseases nowadays; that the account of the treatment of tuberculosis should give more detail regarding regimens suitable in developing countries; that the account of mycobacterial diseases should be updated; and that the space allocated to bronchial asthma should also be increased, the extra pages being gleaned by tidying up some of what might be called the 'fragment' sections.

It does not seem so many years since we were lamenting the dearth of quality textbooks on respiratory medicine. Now there are very good books available for students and clinicians of all levels of experience. This book should be on the bookshelves of all hospital libraries. It bids fair to be amongst the leading textbooks on the subject. Every physician dealing with chest medicine should possess copies of this book and of Crofton and Douglas's *Respiratory Diseases*, 3rd edition, 1981, because they are complementary to each other to a remarkable degree.

N. W. Horne

A Colour Atlas of Respiratory Diseases
D. Geraint James and Peter R. Studdy
London: Wolfe Medical. 1981. 1st edition.
Pp. 272. Price £45

Doctors and their libraries seem to have an insatiable appetite and inexhaustible funds for new books. The torrent of new titles continues to grow, and each book confirms the excellence of its predecessors by imitating them so closely as to be barely distinguishable from them. It is therefore a rare and welcome pleasure to find a book that is genuinely new, different and a real addition to the existing range.

This colour atlas is a collection of 800 pictures and radiographs with brief explanatory captions, each containing a few additional scraps of information about the condition illustrated. There are also a limited number of tables, lists and line drawings. The book falls into two sections: the first teaches normal anatomy, and the reading of chest radiographs, while the second concentrates on specific diseases. Very roughly, one-third of the pictures are radiographs, one-third clinical photographs and one-third histology.

The chief aim of the book is to provide pictorial examples and in this it succeeds splendidly. The illustrations are clear, superbly reproduced and on the whole well selected. The sections on tuberculosis, sarcoidosis and interstitial lung diseases are particularly strong and the disease-orientated chapters are almost impossible to fault. There are minor problems of balance but this is seldom important and clearly the photogenicity of some conditions exceeds their prevalence. (Behçet's disease benefits from more than two pages of lovely pictures while boring bullae get none.)

The more didactic parts of the book are less good. A few of the radiographs intended to illustrate specific abnormalities are misleading and occasionally wrong. Some of the lists contain mistakes (mycoplasma and legionella are classified as viruses) and the attempt to force immunological lung diseases into a simple classification does not work. The flow diagram for the treatment of sarcoidosis shows a personal approach and does not indicate which patients should be treated. However, these failings are not at all important as the book is intended to be used alongside a more comprehensive standard text. It will never be the sole source of information and its appeal is in the pictures not the words.

Overall, the book can be most strongly recommended. It is a singularly painless way to absorb a great deal of information and for many of us our visual memory is understretched while we are battered with too many words. I would recommend all libraries to buy this book and to keep it well chained to the wall.

D. M. Geddes

Lung Function for the Clinician

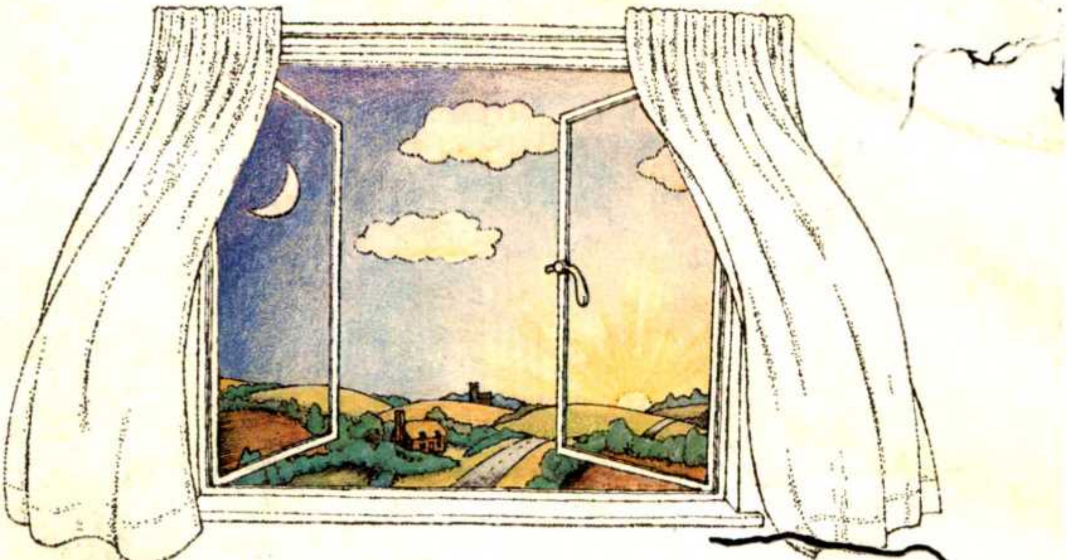
D. T. D. Hughes and D. W. Empey
London: Academic Press/New York: Grune & Stratton. 1981. 1st edition. Pp. x + 122. Price £6.80

This is a simple text offering a useful if rather pedestrian guide to lung function tests in current use. The approach is conventional with descriptions of the basic function of the lung and its investigation by means of straightforward tests. Spirometry, lung volumes, blood gas tensions and diffusing capacity are given appropriate pride of place over more sophisticated tests.

The whole text however is rather archaic and unimaginative. The photographs are of poor quality and some of the equipment illustrated has been superseded by more up-to-date models. For a European audience the use of mm Hg rather than kPa is an anachronism.

There is a sad tendency to 'get lung function tests done' with very little thought concerning the value of the information gained. This book does not encourage a more intelligent approach. It gives too little emphasis on interpretation and on the practical use of tests. The list of applications given in the first chapter could have provided a framework for following up this line of thought but is not developed further.

D. J. Lane



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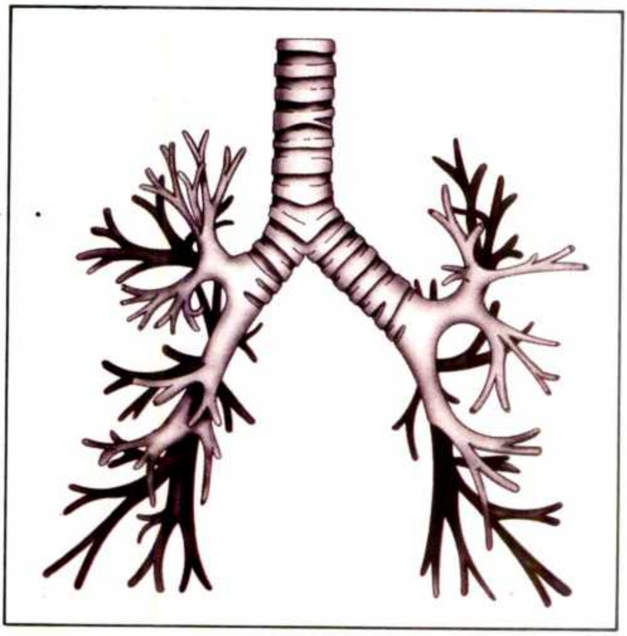

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Br. J. Dis. Chest (1982) *76*, 313

SECONDARY POLYCYTHAEMIA: ITS CAUSES, EFFECTS AND TREATMENT

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Introduction

Polycythaemia can be defined as an increase in the haemoglobin level or packed red cell volume of venous blood. When repeated haematocrit levels exceed 0.50 in males or 0.47 in females, measurements of the red cell mass and plasma volume are indicated (Pearson 1980). These may show a normal red cell mass with a reduced plasma volume; this is pseudopolycythaemia, and occurs with dehydration, diuretic therapy or chronic alcoholism. A truly increased red cell mass associated with a plasma volume which may be normal, increased or decreased occurs in three well-defined groups of disorders. Polycythaemia secondary to hypoxia is the commonest and results from a physiological increase in erythropoietin production. This occurs in chronic lung diseases, mainly chronic airflow obstruction, in cyanotic congenital heart disease, in residents at high altitude, and in individuals who have haemoglobinopathies with increased oxygen affinity. Secondly, polycythaemia may occur as a consequence of a pathological increase in erythropoietin production, the most common causes being carcinoma of the kidney, uterus or brain. Finally, polycythaemia vera is diagnosed after exclusion of secondary causes, and in the presence of the commonly associated features of leucocytosis, thrombocytosis, splenomegaly and raised leucocyte alkaline phosphatase level. This review is concerned with the first of these three groups of true polycythaemia with special emphasis on the polycythaemia which occurs in patients with hypoxic lung disease.

The physiological adaptations to life at high altitude have helped our understanding of the mechanisms of secondary polycythaemia in disease states. We discuss these first. The effects of artificially altering the haematocrit in animals are then reviewed and this is followed by an assessment of the results of therapeutic reduction of haematocrit in humans with severe secondary polycythaemia. We conclude with an analysis of the various methods of treatment and hope this will be useful to the clinician confronted by patients with severe secondary polycythaemia.

Historical Background

Jourdanet (1861) suggested that symptoms appearing at high altitude were the consequence of a decrease in blood oxygenation. Paul Bert in 1878 hinted that this decrease in blood oxygenation should result in an increased number of red cells in the blood. Eleven years later Viault (1889) demonstrated for the first time polycythaemia occurring in inhabitants of the Peruvian Andes at a height of 4392 metres. Many years later, controlled experiments by Dallwig, Kolls and Leowenhart (1915) and by Campbell (1926), demonstrated that the increased haemopoietic activity is a consequence of low oxygen tension alone, and not merely of low barometric pressure.

Vaquez (1892) and Sellier (1896) were among the first to describe the polycythaemia associated with obstructive lung disease. It was always tacitly assumed that the mechanisms involved in the production of polycythaemia in patients with lung disease were similar to those in high altitude residents and were related to a low oxygen tension in the blood. According to Arrillaga (1925) Ayerza seems to have described polycythaemia associated with pulmonary vascular diseases some 25 years earlier. These may have been examples of primary pulmonary hypertension or pulmonary fibrosis. Many authors have noted the association between polycythaemia and congenital heart disease (Weil 1901; Weber & Horner 1911; Todtenhaupt 1927), and the associated finger clubbing and cyanosis is well described from early days (Wright 1911).

The ancient Greeks used phlebotomy to treat a miscellany of diseases, but its use in the treatment of polycythaemia is a more recent event (Hörder 1911). Early work in the field of both primary and secondary polycythaemia is reviewed by Harrop (1928) and Lawrence et al. (1953) and more recently by Balcerzak and Bromberg (1975).

Table I. Adaptations to high altitude

1. Ventilatory	Hyperventilation
2. Haematological	Secondary polycythaemia. Increased r.b.c. 2, 3-DPG and P_{50}
3. Cardiovascular	Increased resting heart rate. Fall in stroke volume after a few days. Cardiac output increases initially and later falls. Pulmonary hypertension.
4. Anatomical	Increased alveolar number and alveolar size in natives.

Hypoxia at High Altitude

Adaptive mechanisms occurring in response to the hypoxia of high altitude are directed towards increasing the availability of oxygen in the tissues. This is effected through pulmonary, cardiac and haematological responses (Table I). Only the ventilatory and haematological aspects will be discussed here.

The ventilatory response to high altitude

The Po_2 of inspired air decreases with increasing altitude. The resulting arterial hypoxaemia induces hyperventilation through stimulation of carotid body chemoreceptors. During the first few days at altitude this response is opposed by a rise in pH of brain extracellular fluid which inhibits the central chemoreceptor drive to ventilation. After about four days the brain extracellular fluid pH returns to normal and hyperventilation continues as a result of the effect of hypoxia on the peripheral chemoreceptors and through a re-setting of the central chemoreceptor sensitivity to CO_2. Over a number of years ventilation will tend to return to, but never reach, sea level values (Rahn & Otis 1949; Weil et al. 1971), and will remain higher than that seen in natives. Thus following a prolonged sojourn at high altitude, and in natives, the ventilatory response to hypoxia becomes attenuated (Chodi 1957; Lefrancois et al. 1968) and it is probable that it is the CO_2 response that is important in maintaining blood gas tensions.

Haematological responses

1. *Polycythaemia.* An increased concentration of red blood cells in the circulation is one of the most important adaptations to the hypoxia of altitude. Plasma volume is normal or decreased but the increase in red cell mass leads to an increase in total blood volume (Sanchez et al. 1970). The increased red cell production is directly proportional to the severity of the hypoxia. Hypoxia causes an increased production of erythropoietin. Elevated erythropoietin levels are found immediately on ascent and although they tend to fall to intermediate levels over a few days as other adaptive mechanisms come into operation the polycythaemic response is not complete for some months (Faura et al. 1969). Shortly after descent to sea level erythropoietin levels become undetectable.

Although polycythaemia is usually found in long term residents at high altitude, this response is occasionally exaggerated (Monge & Monge 1966) and subjects with excessive polycythaemia are more hypoxic than normal high altitude residents (Severinghaus et al. 1966; Peñaloza et al. 1971). These patients with excessive polycythaemia are suffering from Monge's disease (chronic mountain sickness, chronic soroche), and experience decreased exercise tolerance, increased fatigability and frequently headache, dizziness, paraesthesiae and somnolence (Peñaloza et al. 1971). Palliative treatment is with venesection, but definitive treatment involves taking the patients down to sea level. Return to high altitude produces a recurrence of the clinical picture (Peñaloza et al. 1971). There are several possible explanations for this exaggerated polycythaemic response. First, hypoventilation may occur because, as we have seen, prolonged residence at high altitude may result in decreased ventilatory response to hypoxia (Chodi 1957; Lefrancois et al. 1968). Secondly, recent work has shown that polycythaemia occurring at high altitude is associated with an increased physiological dead space (Cruz et al. 1979), a smaller tidal volume and greater ratio of dead space to tidal volume than is seen in normal subjects (Kryger et al. 1978). Interestingly, stimulation of respiration with medroxyprogesterone results in alleviation of the polycythaemia of altitude possibly by increasing the sensitivity of the respiratory centre to hypoxia and improving ventilation perfusion relationships (Kryger et al. 1978). Thirdly, the excessive polycythaemia at altitude is commoner in smokers, in patients with chronic airflow obstruction (Brewer et al. 1970), and in patients with alveolar hypoventilation resulting from obesity or kyphoscoliosis (Arias-Stella 1971). These conditions all produce a further lowering of arterial oxygen tension.

2. *2,3-Diphosphoglycerate (2,3-DPG).* Keys and colleagues (1936) showed that at high altitude the oxygen–haemoglobin dissociation curve shifted to the right, while Aste-Salazar and Hurtado (1944) demonstrated that this was an adaptive response that facilitated O_2 release in the tissues. This shift is now known to be mediated by an increase in intraerythrocyte 2,3-DPG, a substance which decreases oxygen affinity for haemoglobin. Synthesis of 2,3-DPG is increased during anaerobic stress (e.g. exercise, hypoxia), and when there is reduction in available oxygen (e.g. anaemia, congestive heart failure). The increase in 2,3-DPG can occur rapidly, but usually takes one to two days after ascent to high altitude (Lenfant et al. 1968). The increase in 2,3-DPG causes decreased affinity of haemoglobin for O_2 reflected by an increase in the partial pressure of oxygen at which the blood is 50% saturated (increase in P_{50}) and represents an inbuilt mechanism which facilitates the release of O_2 in tissues in response to hypoxia. This mechanism is advantageous only when the alveolar Po_2 is 10 kPa or greater where oxygen is loaded onto haemoglobin in the lungs on the flat part of the oxygen–haemoglobin association curve. Similar changes, in 2,3-DPG levels have been noted in cyanotic congenital heart disease (Woodson et al. 1970), and in some patients with chronic lung disease (Lenfant et al. 1969; Flenley et al. 1975).

3. *Haematological responses in Sherpas.* All the studies so far mentioned on the polycythaemia of altitude have been performed on Peruvian Amerindians. By contrast Sherpas living permanently at high altitude (4000 m) in the Himalayas do not have polycythaemia or increased 2,3-DPG levels, and their haemoglobin shows a higher affinity for oxygen than does that of acclimatized Caucasians (Morpurgo et al. 1976). These authors suggest that Sherpas are genetically better adapted to high altitude than Amerindians in the Peruvian highlands. On the other hand the Peruvian residents, many of whom are involved in mining, also smoke more heavily so that local environmental factors may be contributing to the observed differences. It is unlikely that depression of hypoxic drive alone causes excessive polycythaemia, since despite the similarly blunted hypoxic drive in Andean and Himalayan people excessive polycythaemia is very uncommon in the Himalayas.

The Relationship Between Red Cell Mass and Hypoxia in Patients with Chronic Lung Disease

Erythropoietin secretion which stimulates red cell formation depends on the balance between the supply and demand for oxygen in tissues (Fried et al. 1957; Rørth 1974). At rest there are at least eight factors which determine tissue oxygen delivery (Table II). Arterial oxygen saturation (Sao_2) depends on the first five of these (Pao_2, pH, $Paco_2$, r.b.c. 2,3-DPG, and $Paco$), and patients with hypoxic lung disease may have hypercapnia and often a raised *P*aco as well as hypoxia. Carbon monoxide reduces oxygen delivery by combining with haemoglobin to form carboxyhaemoglobin thereby reducing the blood oxygen carrying capacity (Sagone et al. 1973), and also by increasing the affinity of haemoglobin for oxygen, that is decreasing the P_{50} (Sagone & Balcerzak 1975). Raised carboxyhaemoglobin levels are probably an important contributing factor in the genesis of secondary polycythaemia in some patients with hypoxic lung disease (Balcerzak & Bromberg 1975; Vanuxem et al. 1977; Calverley et al. 1980) and Monge's disease.

The position of the oxygen–haemoglobin association–dissociation curve as measured by P_{50} varies in patients with hypoxic lung disease (Lenfant et al. 1969; Fairweather et al. 1974). Increases in $Pa\text{CO}_2$ and r.b.c. 2,3-DPG and falls in pH all increase the P_{50}, while increases in *P*aco lead to a fall in P_{50}. However the exact position of the curve in severely hypoxic patients probably matters little because the shape of the curve does not vary and their haemoglobin therefore combines with, as well as releases, oxygen on the steep part of the curve.

Table II. Factors involved in tissue oxygen delivery at rest

Arterial oxygen tension
Arterial pH
Arterial carbon dioxide tension
Red cell 2,3-diphosphoglycerate concentration
Carbon monoxide tension
Haemoglobin concentration
Cardiac output
Local tissue blood flow

Of much greater importance when looking at oxygen delivery to the tissues are the changes during sleep and during exercise. Some patients with chronic airways obstruction have profound falls in their already low $Sa\text{O}_2$ and $Pa\text{O}_2$ during sleep (Pierce et al. 1966; Koo et al. 1975; Leitch et al. 1976). These may be associated with sleep apnoea but hypoventilation and falling ventilation perfusion ratios are probably more important factors (Douglas et al. 1979; Catterall et al. 1981). Again during exercise severely hypoxic patients develop a fall in $Pa\text{O}_2$ and in some the rise in cardiac output is subnormal (Segel & Bishop 1966; Filley et al. 1968; Harrison et al. 1973).

The standard method of studying response of the red cell mass to hypoxia is to look at the relationship between red cell mass and resting arterial oxygen saturation ($Sa\text{O}_2$). Obviously, for the reason given above, $Sa\text{O}_2$ is a wholly inadequate way of describing tissue oxygen delivery. In patients with chronic airways obstruction further complicating factors include the effects of recurrent infection which may reduce erythropoiesis (Lertzman et al. 1962; Ayvazian et al. 1969), and of a reduced plasma volume (Harrison 1973) which leads to a relatively higher haematocrit and blood viscosity at any given level of red cell mass.

Weil et al. (1968) described what has been regarded as the normal inverse relationship between resting arterial oxygen saturation and red cell mass (dotted line and hatched area Fig. 1) by studying 73 normal men resident at three separate altitudes (sea level, 1600 m and 3100 m). Several studies in patients with hypoxic lung disease have suggested that the increase in red cell mass is quantitatively the same as that due to high altitude in normal subjects (Shaw & Simpson 1961; Lertzman et al. 1962; Hume 1968; Chan 1969). Others have found a lower than expected response in hypoxic patients (Vanier et al. 1963; Murray 1965; Ayvazian et al. 1969; Cocking & Darke 1972). In addition to the problems already discussed, variation in patient selection and duration of hypoxia are further variables that help explain the lack of agreement in the literature.

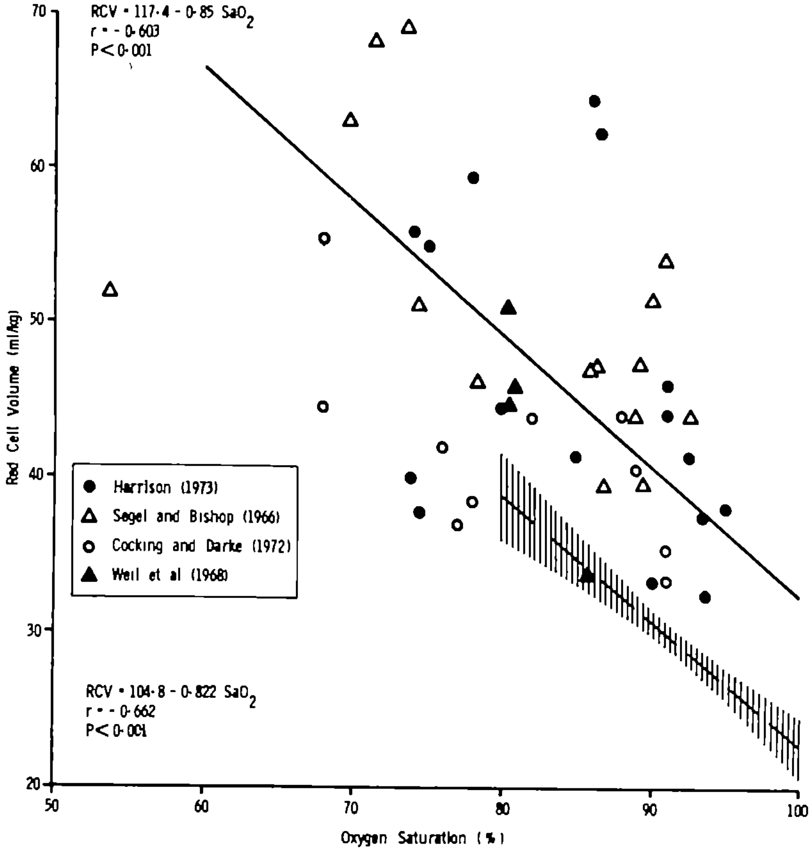

Fig. 1. Relationship between arterial oxgyen saturation and red cell volume in 45 polycythaemic patients with lung disease including 16 patients studied by Harrison (1973) (●), 15 patients studied by Segel and Bishop (1966) (△), 10 patients studied by Cocking and Darke (1972) (○), and four patients studied by Weil et al. (1968) (▲). The continuous line represents the regression line for the patients (RCV = 117.4 − 0.85 SaO_2; $r = -0.603$; $P < 0.001$) and the broken line that found in normal subjects reported by Weil et al. (1968) (RCV = 104.8 − 0.822 SaO_2; $r = -0.662$; $P < 0.001$). The hatched area represents the 95% confidence limits of the relationship in the normal subjects. (Reproduced from Harrison (1973) by permission of the author and publisher)

Figs 1 and 2 illustrate the importance of patient selection. The patients are taken from four studies in which comparable techniques were used. Segel and Bishop (1966) studied 15 patients with chronic bronchitis and secondary polycythaemia; Weil et al. (1968) studied nine patients with chronic airways obstruction whose haematocrit ranged from 0.435 to 0.66; Cocking & Darke (1972) studied 45 patients with chronic obstructive bronchitis; Harrison (1973) studied 19 patients with chronic airways obstruction with a high venous haematocrit (> 0.48 in women and > 0.52 in men). Fig. 1 shows the relationship between red cell mass and arterial oxygen saturation in the 45 patients with measured polycythaemia (red cell mass > 30 ml/kg in women and > 34 ml/kg in men) and Fig. 2 the same relationship in the 43 patients with lung disease who were not polycythaemic. The mean SaO_2 of the 45 polycythaemic patients was 82.6% and was

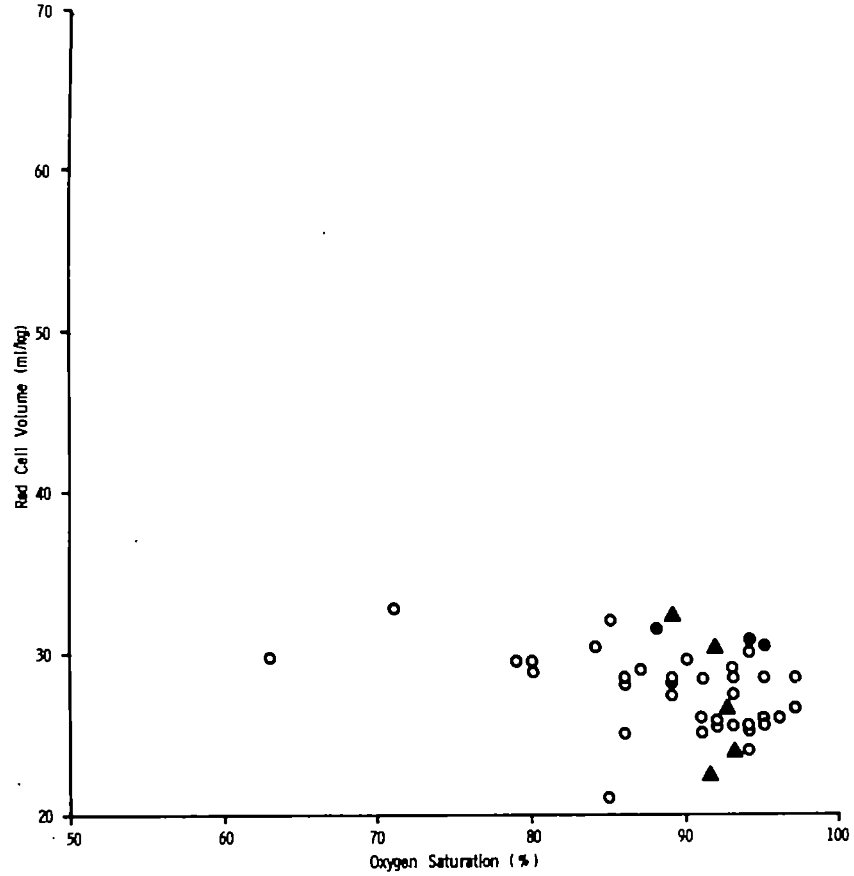

Fig. 2. Relationship between arterial oxygen saturation and red cell volume in 43 patients with lung disease who were not polycythaemic. These patients are from the same series and are represented by the same symbols as those in Fig. 1. There was no significant relationship between arterial oxygen saturation and red cell volume. (Reproduced from Harrison (1973) by permission of the author and publisher)

significantly lower than the mean $Sa{O_2}$ of the other 43 patients which was 90.1% ($P < 0.001$). For these reasons it is unreasonable to expect a close correlation between red cell mass and resting arterial oxygen saturation in these patients (Harrison 1973; Stradling & Lane 1981). However there does appear to be a small group of patients with lung disease who are severely hypoxic who develop an extreme degree of secondary polycythaemia (Fig. 1). The existence of the large numbers of patients who, though hypoxic, do not develop secondary polycythaemia may be related to the variable factors discussed above or to other unknown factors. A reliable and sensitive haemopoietin assay would help unravel some of these problems.

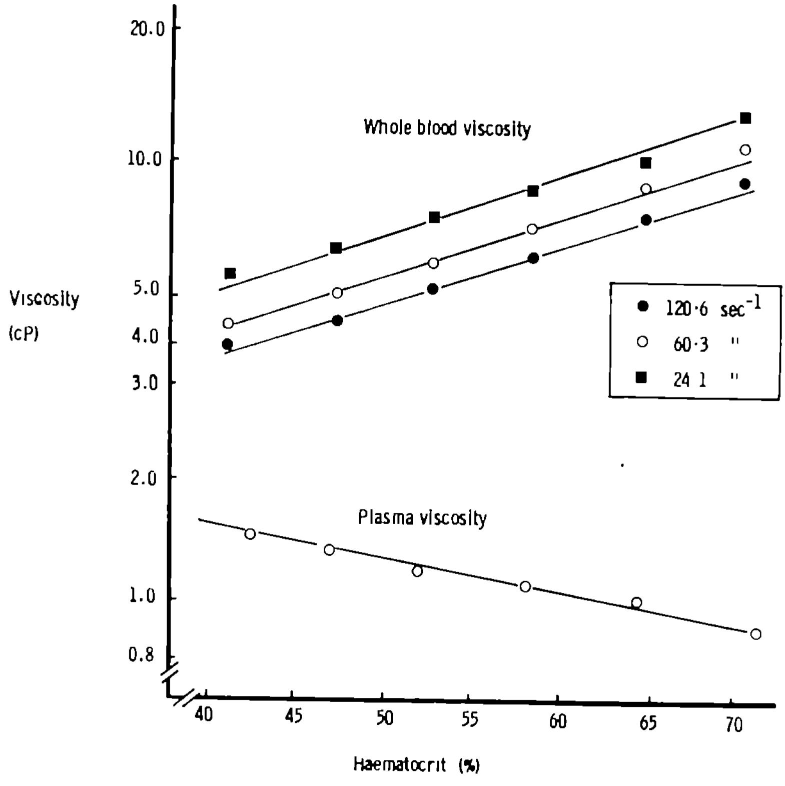

Fig. 3. Changes in whole blood viscosity and plasma viscosity during isovolaemic haemodilution by means of dextran 60 in dogs (mean values). (Reproduced from Sunder-Plassman et al. (1970) by permission of the authors and publisher)

In Vitro and Animal Experiments on the Relationship between Haematocrit, Blood Viscosity, Vascular Resistance and Tissue Oxygen Delivery

The relationship between increasing haematocrit and blood viscosity in vitro is an exponential one (Dintenfass & Read 1968; Dormandy 1970; Sunder-Plassmann et al. 1970) (Fig. 3). Dintenfass and Read (1968) have shown that hypoxia not only stimulates red cell production but increases the internal viscosity and the agregation of red cells. They showed that acidosis also increases the internal viscosity of the red cells and that infection both increases the plasma globulins and facilitates red cell aggregation. All may contribute to an increased blood viscosity in patients with chronic lung disease and hypoxia.

The effects of rising haematocrit on the systemic and pulmonary circulation of the dog have been studied by Levy and Share (1953) and Agarwal et al. (1970). Levy and Share (1953) perfused the denervated hind limb of the dog with blood of varying haematocrits. They measured the pressure drop across the circulation and the blood flow. We have replotted the results of one of their experiments in Fig. 4 to show the relationship between haematocrit and pressure drop across the circulation at a constant blood flow of 29 millilitres per minute. This exponential increase in pressure with rising haematocrit occurred at flows ranging from 10 to 150 millilitres per minute. They also found an exponential increase in blood viscosity with increasing haematocrit both in vitro and in vivo. In the pulmonary circulation of the dog Agarwal et al. (1970) have demonstrated a similar exponen-

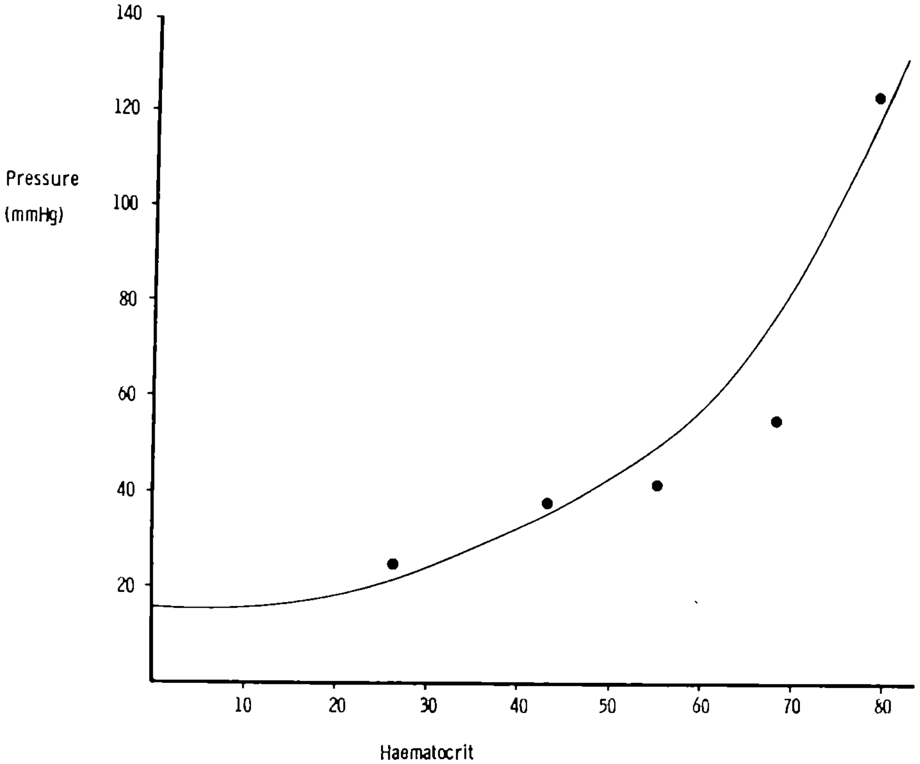

Fig. 4 Relationship between the haematocrit and the pressure drop across the circulation at a constant blood flow of 29 millilitres per minute in the denervated hind limb of the dog. (Replotted from the results of Levy and Share (1953) by permission of the authors and the American Heart Association, Inc.)

tial increase in pressure drop across the capillary bed at constant blood flow with rising haematocrit. They maintained a constant pulmonary blood flow and alveolar pressure while making their measurements. Fig. 5 illustrates an exponential increase in pulmonary vascular resistance with rising haematocrit in a series of experiments performed in six dogs at four different left atrial pressures.

Replogle and Merrill (1970) studied the effects of rising haematocrit on oxygen delivery to the tissues. In anaesthetized dogs they induced normovolaemic polycythaemia by exchanging packed cells for whole blood, and then returned the dogs to their original haematocrit. Measurements were made before exchange transfusion, 30–60 minutes after reaching the polycythaemic state, and again 30–60 minutes after returning to the original haematocrit. Their results are summarized in Table III. These show that in the acutely induced polycythaemic state, despite the increased oxygen carrying capacity, red cell ejection from the left ventricle and peripheral oxygen consumption fell and the lactate pyruvate ratio rose. These changes, which were reversible (Table III), suggested a shift towards a more anaerobic phase of metabolism perhaps reflecting decreased peripheral tissue perfusion. Other workers have also reported a reduction in systemic oxygen output (the product of cardiac output and arterial oxygen content) as a consequence of polycythaemia indicating that the increased oxygen

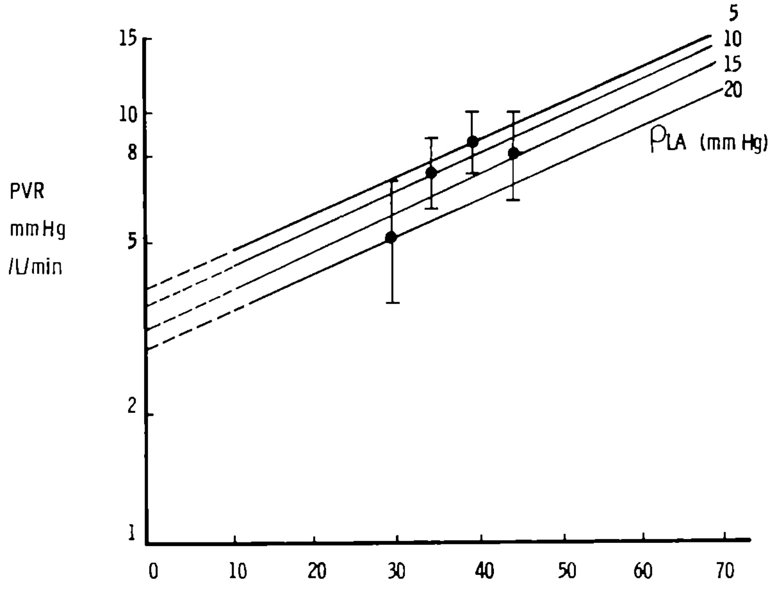

Fig. 5. Regression lines for the effect of haematocrit on pulmonary vascular resistance (PVR) at various levels of left atrial pressure (P_{la}) at a constant pulmonary blood flow and alveolar pressure. Pooled data from six experiments. Vertical bars represent ± one standard error of regression estimate. Dashed lines indicate extrapolation to zero haematocrit. (Reproduced from Agarwal et al. (1970) by permission of the authors and publisher)

carrying capacity of polycythaemic blood does not compensate for the fall in cardiac output that accompanies the induced polycythaemia (Richardson & Guyton 1959; Murray et al. 1962; Weisse et al. 1964; Sunder-Plassmann et al. 1970).

These in vitro and animal experiments indicate that in severe degrees of polycythaemia the advantages of increased oxygen carrying capacity are more than offset by the increased blood viscosity and the deteriorating flow properties of the blood. Acutely polycythaemic animals demonstrate an increased systemic and pulmonary vascular resistance and a shift of their respiration to a more anaerobic phase. Such acute laboratory experiments are clearly far removed from the breathless cyanosed patients with ventilatory failure, cor pulmonale, and chronic secondary polycythaemia. Before turning to measurements in such patients we will briefly review the clinical evidence that severe degrees of secondary polycythaemia are harmful.

Table III. Cardiac output, haematological and metabolic changes after acutely induced isovolaemic polycythaemia and subsequent haemodilution in 20 anaesthetized dogs*

	Control	*Polycythaemia*	*Haemodilution*
Cardiac output (ml/min)	1457 ± 338	505 ± 240	1793 ± 404
Haematocrit (%)	38 ± 5.3	60.5 ± 6.1	33 ± 5.2
Lactate/pyruvate ratio	15.3 ± 3.3	25 ± 9.2	13.3 ± 2.2
Peripheral oxygen consumption (ml/min)	58.7 ± 16.8	36.3 ± 12.0	68.3 ± 13.3
Viscosity at $0.1\,\text{sec}^{-1}$ (centipoise)	69.1 ± 36.8	244 ± 105	66.1 ± 29.7
Red cell ejection (ml/min)	554	304	592

* Adapted from Replogle and Merrill (1979) with permission of authors and publishers.

Clinical Effects of Secondary Polycythaemia in Chronic Lung Disease

Right ventricular hypertrophy and right heart failure are both commoner in patients with chronic lung disease who have developed a raised venous haematocrit. Renzetti et al. (1966) found the incidence of right heart failure to be 53.8% in patients with haematocrits over 54% but only 16.4% in patients with haematocrits below 54%. Semmens (1971) found in necropsy studies on patients with chronic airways obstruction that all those with haematocrits greater than 51% had right ventricular hypertrophy. Mitchell et al. (1964) reported an increased mortality in patients with chronic airways obstruction and a raised venous haematocrit. Many authors (Chamberlain & Millard 1963; Segel & Bishop 1966; Pengelly 1966, 1969; Gregory 1971; Harrison et al. 1971; Dayton et al. 1975; York et al. 1980) have commented on the presence in patients with secondary polycythaemia of symptoms attributable to hyperviscosity, including somnolence, lethargy, poor concentration and headache, symptoms which are often relieved when the haematocrit is reduced. The parallels with Monge's disease or chronic mountain sickness are close. It must be pointed out that no studies have attempted to quantify these symptoms.

Investigations into the Physiological Effects of Reducing Blood Volume and Haematocrit in Patients with Secondary Polycythaemia

Early studies of the effects of venesection on haemodynamics and on pulmonary function in patients with lung disease and secondary polycythaemia proved inconclusive. Auchincloss and Duggan (1957) demonstrated no overall changes in pulmonary function or haemodynamics after venesection. Rakita et al. (1965) studied 15 patients with haematocrits over 0.50 before, immediately after, and five to six weeks after venesection. The later follow-up studies showed no overall change in pulmonary function or haemodynamics although there was a significant fall in blood viscosity and oxygen carrying capacity. Both groups of investigators noted an increase in arterial oxygen saturation immediately after venesection. Rakita et al. (1965) also observed a fall in exercise minute ventilation five to six weeks after venesection. A later study by Segel and Bishop (1966) on the effects of venesection on the circulation in patients with chronic airways obstruction and secondary polycythaemia is important. They investigated 15 patients all of whom

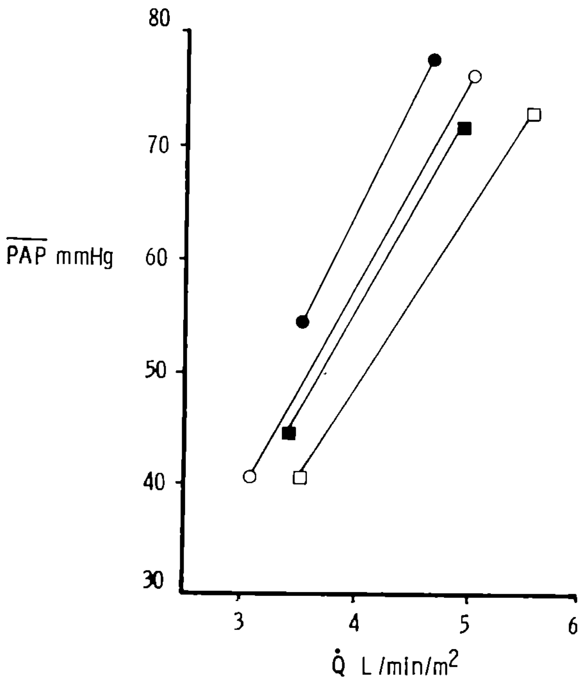

Fig. 6. Relationship between cardiac index ($\dot{Q}$) and mean pulmonary artery pressure ($\overline{PAP}$) at rest and during exercise before (circles) and after (squares) therapeutic venesection. The data are taken from Segel & Bishop (1966). Patients have been separated into two groups. One group of six patients had a fall in whole blood volume after treatment of 6 ml/kg or greater (range −6.0 to −25.3 ml/kg) (solid symbols). The other group of eight patients had a fall in whole blood volume after treatment of 5.1 ml/kg or less (range −5.1 to +4.3 ml/kg) (open symbols). (Data reproduced by permission of the authors and publisher)

had measured polycythaemia: 10 with haematocrits of 0.60 or greater, two with haematocrits of 0.58 and three with values of 0.55, 0.54 and 0.51. All patients were in a stable condition before the study, were free of oedema and their weights were steady. After the initial studies the haematocrit was reduced to a mean value of 0.44 by a series of small venesections and the blood gas, haemodynamic and blood volume measurements were repeated at least 36 hours after the final venesection. There were no changes in arterial blood gases either at rest or during exercise. They observed a fall in pulmonary artery pressure and pulmonary vascular resistance (calculated as the difference between mean pulmonary artery and mean pulmonary wedge pressures divided by cardiac output) but no change in cardiac output at rest or during exercise. For the group they found the expected large fall in red cell volume, a definite but smaller increase in plasma volume and hence a fall in whole blood volume. They concluded that it was this fall in whole blood volume which was the major cause of the haemodynamic changes and that the effects of the fall in blood viscosity were relatively trivial.

This question of whether the haemodynamic benefits are related entirely to the fall in whole blood volume or to the combined effect of a fall in whole blood volume and a fall in haematocrit is an important one. We have plotted the results from 14 patients from Segel and Bishop's study in Fig. 6, separating six patients with falls in whole blood volume after venesection of 6 millilitres per kilogram or greater (range of fall: 6.0–25.3 ml/kg, mean 14.6 ml/kg) from eight patients whose fall in whole blood volume was less than 6 millilitres per kilogram or whose whole blood volume rose (range: −5.1 to +4.3 ml/kg, mean fall 2.16 ml/kg). The group with the large fall in blood volume in addition to a fall in haematocrit shows greater falls in pulmonary artery pressure and pulmonary vascular resistance (Table IV). However, the eight patients with very little change in circulating blood volume also show a fall in pulmonary artery pressure on exercise ($P < 0.02$) and falls in pulmonary vascular resistance at rest and on exercise. Although the numbers in each group are small it seems likely that falls in blood volume and in haematocrit are both important in contributing to the fall in pulmonary artery pressure and pulmonary vascular resistance in this group of patients.

Harrison et al. (1973) reported studies in 10 patients selected using criteria similar to those of Segel and Bishop (1966); eight had haematocrits of 0.60 or greater and two had haematocrits of 0.59 and 0.55. Again, all patients were in a stable state without signs of infection or fluid retention and their weights were steady. Measurements were made before and at least three days after therapeutic reduction of haematocrit. Earlier reports that this treatment had no effect on static or dynamic lung volumes, blood gases or pH at rest or during exercise were confirmed. Measurements at rest and during steady-state seated exercise before and after treatment in four of their patients showed an elevated pulmonary artery pressure at rest which rose abnormally on exercise. Cardiac output was higher on exercise after treatment despite a fall in whole blood volume in all patients. At this higher cardiac output pulmonary artery pressure was little changed indicating a decrease in pulmonary vascular resistance. They concluded that this was probably explained by a change in the flow properties of the blood.

In the same paper these authors reported results of progressive exercise tests in this group of patients and these results have now been extended to include 11 patients (Fig. 7). Patients exercised at progressively increased work loads on a cycle ergometer until they could go no further. Duplicate tests were performed before and after treatment except in one man (patient 4) in whom the pretreatment test was stopped because of the development of ventricular extrasystoles. Nine patients, (represented by solid circles) claimed subjective improvement and in six there was a marked increase in work performed after treatment. Two patients derived no benefit from therapeutic reduction in their haematocrit. One noticed no subjective change but performed less work after treatment and a subsequent chest radiograph showed that a pneumothorax had developed. The other said he felt worse after treatment and he too performed less work. He had

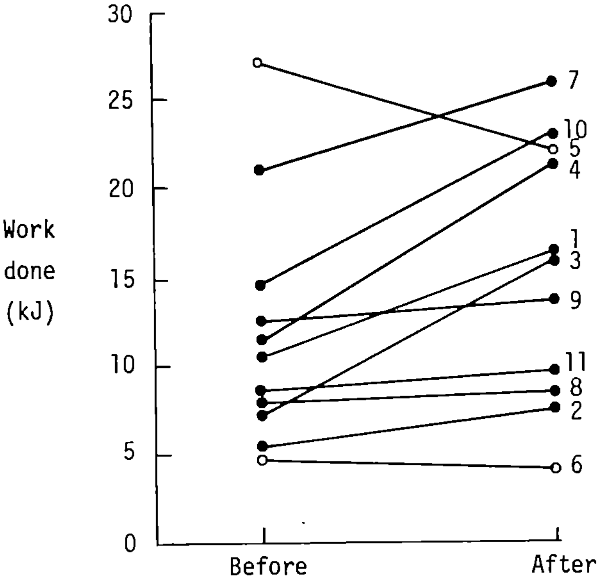

Fig. 7. The work performed during progressive exercise before and after decrease of haematocrit in 11 patients. Solid circles represent nine patients subjectively improved after treatment. Open circles represent two patients not benefited by the treatment (Adapted from Harrison et al. (1973) by permission of the authors and publisher)

the lowest pretreatment haematocrit of 0.55 and a haematocrit after treatment of 0.40 which we would now regard as too low. It should be emphasized that the increased attention these patients receive during such a study, followed by the impressive bleeding procedure, may induce a subjective well-being which might improve exercise performance.

Weisse et al. (1975) reported a further study of 12 patients with hypoxic lung disease and secondary polycythaemia selected and studied in a very similar way to those of Segel and Bishop (1966): seven had initial haematocrits of 0.60 or greater, two had haematocrits of 0.59 and three haematocrits of 0.57. Patients were in a stable clinical state with steady weights before the pretreatment investigations.

The mean pretreatment haematocrit was 0.61 (Stage I); haemodynamic measurements were repeated when the haematocrit had fallen to 0.50 (Stage II) and then again when it had fallen to 0.44 (Stage III) as a result of repeated venesections. Post-treatment studies were performed no sooner than 48 hours after the last venesection. From Stages I to III there was a significant fall in mean pulmonary artery pressure and from Stages I to II and I to III significant falls in total pulmonary resistance (calculated from mean pulmonary artery pressure divided by cardiac output) but no significant changes in cardiac output. All these studies

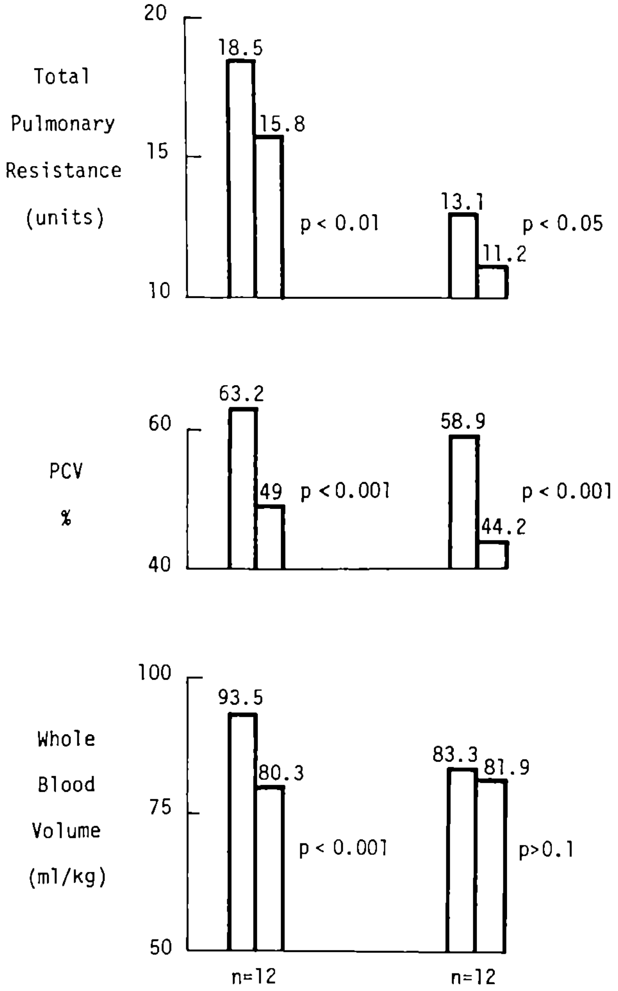

Fig. 8. Changes in total pulmonary resistance, haematocrit, and whole blood volume in two groups of patients before and after therapeutic venesection. The left-hand columns show results from 12 patients whose whole blood volumes fell by 6 ml/kg or more. The right-hand columns show results from 12 patients whose whole blood volumes fell by less than 6 ml/kg or actually increased. (Results calculated from data by Segel and Bishop (1966) and Weisse et al. (1975) by permission of the authors and publishers. See text for further details)

were performed resting in the supine position. No significant haemodynamic changes occurred between Stages II and III. The overall blood volume changes after treatment were less than in the patients studied by Segel and Bishop (1966) and the slight falls in the whole blood volume between Stages I and II and I and III were not significant.

We have attempted to explore the problems of whether the haemodynamic improvements measured in these studies result from the fall in whole blood volume, the fall in haematocrit or both, by combining the data from the studies performed by Segel and Bishop (1966) and Weisse et al. (1975). The patients have been divided into two groups (Fig. 8). Group 1 (left-hand column) consists of 12 patients whose blood volumes after repeated venesection fell by 6 millilitres per kilogram or more (range −6.0 to −25.3 ml/kg) because their plasma volumes either remained unchanged or increased by much less than the therapeutic fall in red cell volume. Group 2 (right-hand column) consists of 12 patients whose blood volumes fell by less than 6 millilitres per kilogram (range −5.1 to +4.3 ml/kg). In this group plasma volume increased by an amount similar to the fall in red cell volume, resulting in little or no overall change in whole blood volume. The two patients from the series of Weisse et al. (1975) whose blood volumes increased by 7 and 12 millilitres per kilogram have not been included. We have calculated total pulmonary resistance at rest for each group. In group 1, where there is a fall in whole blood volume and haematocrit, there was a large fall in total pulmonary resistance. In group 2, where the whole blood volume remains unchanged, there was a smaller but still significant fall in total pulmonary resistance.

We conclude that the haemodynamic effects of a therapeutic reduction in haematocrit in patients with severe degrees of secondary polycythaemia bring about an important reduction in pulmonary vascular resistance and often in pulmonary artery pressure. This is due to the fall in haematocrit and blood viscosity and, *when it occurs,* to the fall in whole blood volume. Both act in the same direction.

Oxygen Delivery and Metabolic Function during Exercise Before and After Haematocrit Reduction in Patients with Secondary Polycythaemia

Oxygen consumption during the same level of steady-state exercise has been shown to increase by 15% in eight out of nine patients subjectively improved by phlebotomy, although the changes were not statistically significant (Harrison et al. 1973). More conclusive results have been reported by Oldershaw and St John Sutton (1980) in patients with cyanotic congenital heart disease. Systemic oxygen output from the left ventricle was unchanged on exercise following phlebotomy, but there was a fall in mixed venous oxygen tension ($P\bar{v}O_2$) (Harrison et al. 1973). This increased oxygen consumption is of the same order as that found when normal men breathing 11% oxygen during exercise were subsequently exercised at the same work load breathing room air (Naimark et al. 1965), and when patients with chronic lung disease were exercised breathing room air and then 30% oxygen at the same work loads (King et al. 1973).

The combination of increased oxygen consumption, maintained systemic oxygen output and falling $P\bar{v}O_2$, suggests that reduction of haematocrit is associated with increased extraction of oxygen from the blood, possibly as a result of improved tissue capillary perfusion and oxygen delivery.

Cerebral Blood Flow in Polycythaemia and the Effects of Phlebotomy

We have already commented on the subjective improvement in the symptoms associated with hyperviscosity of many patients with severe secondary polycythaemia following therapeutic reduction of haematocrit. This improvement cannot result from changes in cardiac output or arterial blood gases since these alter very little after treatment and most authors have attributed them to lowering of blood viscosity and increased tissue perfusion. Thomas et al. (1977) studied patients with primary polycythaemia and measured a 73% increase in cerebral blood flow (CBF) when haematocrit was reduced by repeated venesection from 0.53 to 0.45. The increase in CBF was highly correlated with blood viscosity. More recently, York et al. (1980) have studied patients with hypoxic lung disease and secondary polycythaemia and found a statistically significant increase in CBF

Table V. Haematological and cerebral blood flow changes in eight patients with lung disease and secondary polycythaemia before and after therapeutic venesections*

Patient number		*Haemoglobin* (gm/dl)	*PCV*	*Cerebral blood flow* (ml/min per 100 g brain tissue)
1	Before	17.7	0.57	33
	After	15.9	0.51	42
2	Before	19.1	0.58	30.4
	After	15.8	0.46	39
3	Before	18.5	0.57	30
	After	16.5	0.47	40.7
4	Before	19	0.60	57
	After	16	0.49	77
5	Before	17.5	0.54	60
	After	16.2	0.47	56
6	Before	19	0.60	29.9
	After	16	0.52	34.3
7	Before	19.2	0.68	43
	After	17.4	0.61	40
8	Before	19.1	0.65	34.5
	After	12.3	0.43	48.3
Mean	Before	18.6	59.8	39.6
	After	15.7	49.5	47.1
		$P < 0.001$	$P < 0.001$	$P < 0.025$

*Stokes et al., unpublished observations.

of 78% after reduction of haematocrit from 0.59 to 0.43. They observed subjective improvement in all patients but no changes in blood gases or pulmonary function, and attributed the improvement in CBF to the measured fall in blood viscosity. In another study of eight patients with polycythaemia secondary to chronic airflow obstruction (Table V) a less marked but significant increase in CBF has been shown to occur when haematocrit is reduced from 0.58 or more to less than 0.50 (Stokes, Thomas & Marshall – unpublished observations). These findings have recently been confirmed by Wade et al. (1981), and shown to be associated with symptomatic improvement.

It is possible that viscosity and haematocrit may not be the only factors responsible for increased CBF following venesection, since Betz (1972) in an extensive review has pointed out that tissue pH may be an important determinant of CBF in such a vital organ. Whatever the mechanims, this increase in CBF is likely to be a contributing factor to the increased sense of well-being experienced by polycythaemic patients following phlebotomy.

Phlebotomy in Cyanotic Congenital Heart Disease (CCHD)

In patients with CCHD red cell mass is increased while plasma volume is usually normal or reduced (Verel 1961; Rosenthal et al. 1971). Increases in blood volume, are therefore due to an increased red cell mass, which is inversely proportional to $Sa\text{O}_2$ (Rosenthal et al. 1971). Polycythaemia in patients with CCHD while generally beneficial can be of such severity as to induce adverse physiological effects in terms of cardiac output and oxygen transport. Venous haematocrits well in excess of 0.68 are found (Veral 1961; Rosenthal et al. 1970), and are associated with thrombotic lesions of lungs (Ferencz 1960), CNS and kidneys (Berthrong & Sabiston 1951) as well as haemorrhagic diatheses (Dennis et al. 1967). Symptoms of lethargy, headache, tiredness and difficulty in concentration are also present.

Patients with CCHD are similar to high altitude residents in that they show a blunted response to hypoxia (Edelman et al. 1970), which may reverse when the hypoxia is surgically corrected and obviously this is the treatment of choice if at all possible for these patients. In patients not amenable to surgery phlebotomy may improve symptoms and haemodynamic disturbances. Although there are no studies which objectively quantitate an improvement in symptoms two groups have investigated the haemodynamic effects of venesection in CCHD. Rosenthal et al. (1970) reduced the mean haematocrit from 0.73 to 0.62 and replaced the volume of blood removed by an equal volume of fresh plasma or 5% albumin. They observed an increase in stroke volume, systemic blood flow and systemic oxygen transport at rest, and emphasized the importance of maintaining hypervolaemia. This was an acute study and did not determine how long this improvement in oxygen delivery persisted. The mean age of their patients was 12.5 years (range 3.5–25 years).

In a more recent acute study Oldershaw and St John Sutton (1980) have studied the effects of venesection while maintaining the blood volume with plasma infusion. The mean PCV was 0.66 before and 0.58 at three days and remained at this value until 14 days after venesection. The resting cardiac output was increased with a non-significant increase in oxygen consumption at three and 14 days following treatment. During the sixth minute of steady-state exercise cardiac output and oxygen uptake were both significantly increased. The mean age of the patients in this study was 22 years (range 15–39 years). Thus patients with CCHD usually have a more severe degree of polycythaemia than those with hypoxic lung disease. Haemodynamic and possibly symptomatic improvement is seen even though the haematocrit is still relatively high after exchange transfusion.

Polycythaemia due to Haemoglobinopathy

Since the first description (Charache et al. 1966) a number of inherited haemoglobin variants showing high affinity for oxygen and consequent secondary polycythaemia have been described (Nagel & Bookchin 1974; Adamson 1975). The conditions may be suspected by the finding of polycythaemia in the presence of normal leucocyte and platelet count, normal blood gases and the absence of splenomegaly. An abnormal band is found on haemoglobin electrophoresis and the oxygen dissociation curve shows a marked leftward shift with very low P_{50} values. The PCV is usually less than 0.56, although individual high levels of PCV and haemoglobin are reported. These conditions appear to be rare, relatively benign, and phlebotomy is seldom indicated.

Methods used to Lower Haematocrit in Severe Secondary Polycythaemia (Table VI)

Repeated simple venesection is the most commonly used method (Auchincloss & Duggan 1957; Rakita et al. 1965; Segel & Bishop 1966; Dayton et al. 1975; Weisse et al. 1975; York et al. 1980), 200–500 millilitres of blood being withdrawn from an antecubital vein. The procedure is repeated at 48 hour intervals until the desired haematocrit is attained. The potential dangers of venesection without volume replacement have been emphasized (Kiraly et al. 1976). Chamberlain and Millard (1963) had seen one patient who developed a fatal pulmonary artery thrombosis following repeated venesection and they adopted the logical approach of giving their patients continuous oxygen in hospital for six weeks. Their patients with secondary polycythaemia all responded with a fall in haematocrit and with symptomatic improvement. However six weeks' oxygen therapy in hospital is both time consuming and expensive. It is interesting that in the two

Table VI. Methods used to lower haematocrit

1. Repeated simple venesection
2. Continuous oxygen for six weeks
3. Drugs to induce haemolysis and bone marrow suppression
4. Exchange transfusion

recent multicentre studies of long term domiciliary oxygen therapy one showed only slight reduction in haematocrit or red cell mass (MRC Working Party 1981) while the other (Nocturnal Oxygen Therapy Trial 1981) showed no change in haematocrit for the first six months, and at 18 months those breathing oxygen for more than 18 hours daily had their haematocrits reduced by only 9%.

Pengelly (1966, 1969) adopted another approach. In his first study he used a combination of dapsone to reduce red cell survival and pyrimethamine to depress erythropoiesis. This was effective in reducing haematocrit though it sometimes proved difficult to titrate the doses of the drugs to the individual patient and some patients became anaemic, while others developed thrombocytopenia. Both were reversible. In the later study he reported successful use of a combination of phenylhydrazine hydrochloride and pryimethamine.

Gregory (1971) described a modification of the technique of simple venesection which he called exchange transfusion and this was the method used by Harrison et al. (1971, 1973) in their studies. Ideally red cell mass is measured first and then sufficient blood is removed from one arm to reduce the red cell mass to normal. A volume of dextran 40 in 5% dextrose equal to half the volume of the venesection is infused into the other arm during the course of the venesection followed by the same volume of dextran over the next 8–12 hours (Table VII). The hypertonic dextran solution draws into the intravascular space approximately its own volume of fluid from the extravascular space. This effect lasts for at least five hours and continuation of the infusion as described allows for the natural replenishment of the intravascular volume. This technique maintains intravascular volume and allows removal of up to 3 litres of blood at once. No ill effects from hypovolaemia have been reported though a few patients have experienced anaphylactic reactions to dextran. Plasma is an alternative replacement solution. Muscle cramps are a fairly common but transient side effect of large exchanges.

Table VII. Example of exchange transfusion

1. Remove 1 litre blood by venesection
2. Infuse 0.5 litre dextran 40 in 5% dextrose simultaneously
3. Then infuse 0.5 litre dextran 40 over next 8–12 hours

(Plasma can be used as an alternative to dextran)

Schaanning and Sparr (1974) comparing the effects of simple venesection of half a litre in one group of patients with exchange transfusion of half a litre in another showed that venesection alone led to an immediate and considerable fall in cardiac output and systemic oxygen output from the left ventricle, while cardiac output increased immediately after exchange transfusion and systemic oxygen output was unchanged.

There are a few technical points. The blood flows more easily if the needle is inserted into the vein with its tip pointing towards the hand rather than towards the heart. The needle may require flushing with saline to ensure continued satisfactory blood flow. Repeated venesection or exchange transfusion may lead to the development of hypochromic polycythaemia which is not accompanied by increased oxygen carrying capacity while the iron deficiency itself increases blood viscosity (Hutton 1979). All patients undergoing therapeutic phlebotomy should receive prophylactic oral iron.

Selection of Patients

Which patients with secondary polycythaemia are likely to benefit from a reduction in their haematocrit? Harrison et al. (1971) reported that all patients with initial haematocrits greater than 0.60 benefited and that some but not all patients with lower haematocrits also improved. Weisse et al. (1975) demonstrated significant falls in mean pulmonary artery pressure and total pulmonary resistance when haematocrit was reduced from a mean of 0.61 to a mean of 0.50 but no further changes of significance when the haematocrit was lowered to a mean of 0.44. We recommend a therapeutic reduction in haematocrit in all patients with values of 0.60 or greater, and we aim to reduce the haematocrit to around 0.50. Dayton et al. (1975) in a double blind study reported symptomatic improvement in eight of 11 patients treated by venesection, but failed to show improvement in resting lung function, blood gases or exercise performance. Although six of the eight responders had pretreatment haematocrits greater than 0.60 the post-treatment haematocrit fell below 0.59 (to 0.55) in only one of these, while the three non-responders had haematocrits of 0.58, 0.56 and 0.53. The results of their study might have been more conclusive if they had recorded what they meant by symptomatic improvement, and if all their patients had had post-treatment haematocrits of 0.50 or less.

Some Outstanding Problems

The problem of why certain patients with hypoxic lung disease develop secondary polycythaemia while others do not has been referred to already and some possible explanations discussed. The development of a reliable erythropoietin assay and the increased availability of measurements during sleep and of carboxyhaemoglobin estimations should help unravel this problem.

A related problem is the recurrence of polycythaemia following therapeutic reduction. In some patients this occurs slowly over months or years or apparently not at all, while in others haematocrits over 0.60 can recur within six to eight weeks.

While many workers comment upon the improvement in well-being reported by patients after treatment no attempts to measure this improvement have been published. Furthermore no-one appears to have extended the idea behind the study of Dayton et al. (1975) of looking at the placebo effect of an adequate reduction in haematocrit with particular respect to exercise tolerance and subjective well-being.

Conclusions

Evidence from in vitro and animal experiments suggests that the increasing blood viscosity associated with increasing haematocrit has deleterious effects on the circulation. The effects of therapeutic reduction of haematocrit in patients are summarized in Table VIII. Measurable improvements have been documented in pulmonary haemodynamics, cerebral blood flow, and exercise tolerance. Patients with haematocrits of 0.60 or greater might be expected to benefit from a therapeutic reduction in their haematocrit. Repeated simple venesection or exchange transfusion with dextran 40 or plasma are the easiest methods of treatment and the aim is to produce an haematocrit of 0.50 or just below, preventing iron deficiency by prescribing prophylactic oral iron therapy.

Table VIII. Summary of the effects of therapeutic reduction of haematocrit in patients with hypoxic lung disease and secondary polycythaemia

1. There is a fall in pulmonary vascular resistance and often in pulmonary artery pressure which results from the reduction in haematocrit and, when it occurs, from the fall in whole blood volume as well.
2. There is an increase in exercise tolerance as measured by progressive exercise on a cycle ergometer in patients who derive subjective benefit from the treatment.
3. There is an increase in cerebral blood flow after treatment.
4. There are no significant changes in blood gases or pH either at rest or during exercise when these are measured at least 36 hours after the last treatment, though there is an increase in arterial oxygen tension one hour after treatment.
5. There are no significant changes in static or dynamic lung volumes

The commonest group of patients with such severe degrees of secondary polycythaemia have severe airways obstruction with FEV_1 less than 1 litre, hyperinflated lungs and hypercapnia as well as hypoxaemia. They are, therefore, very disabled and the prognosis is poor. Therapeutic reduction in haematocrit is a worthwhile form of treatment with measured objective benefit and reported subjective benefit. It is unknown whether this therapy has any effect on prognosis, but it would seem to be an acceptable adjunct to domiciliary oxygen therapy and to pulmonary vasodilators, recently shown to have possible therapeutic benefit (Simonneau et al. 1981). We, therefore, disagree with a recent Royal College of Physicians report (A Report of the Royal College of Physicians on Thoracic Medicine 1981), which concluded that treatment of severe degrees of secondary polycythaemia is of unproven benefit. The evidence presented here supports our view, and we hope it offers helpful guidelines in the management of this group of patients.

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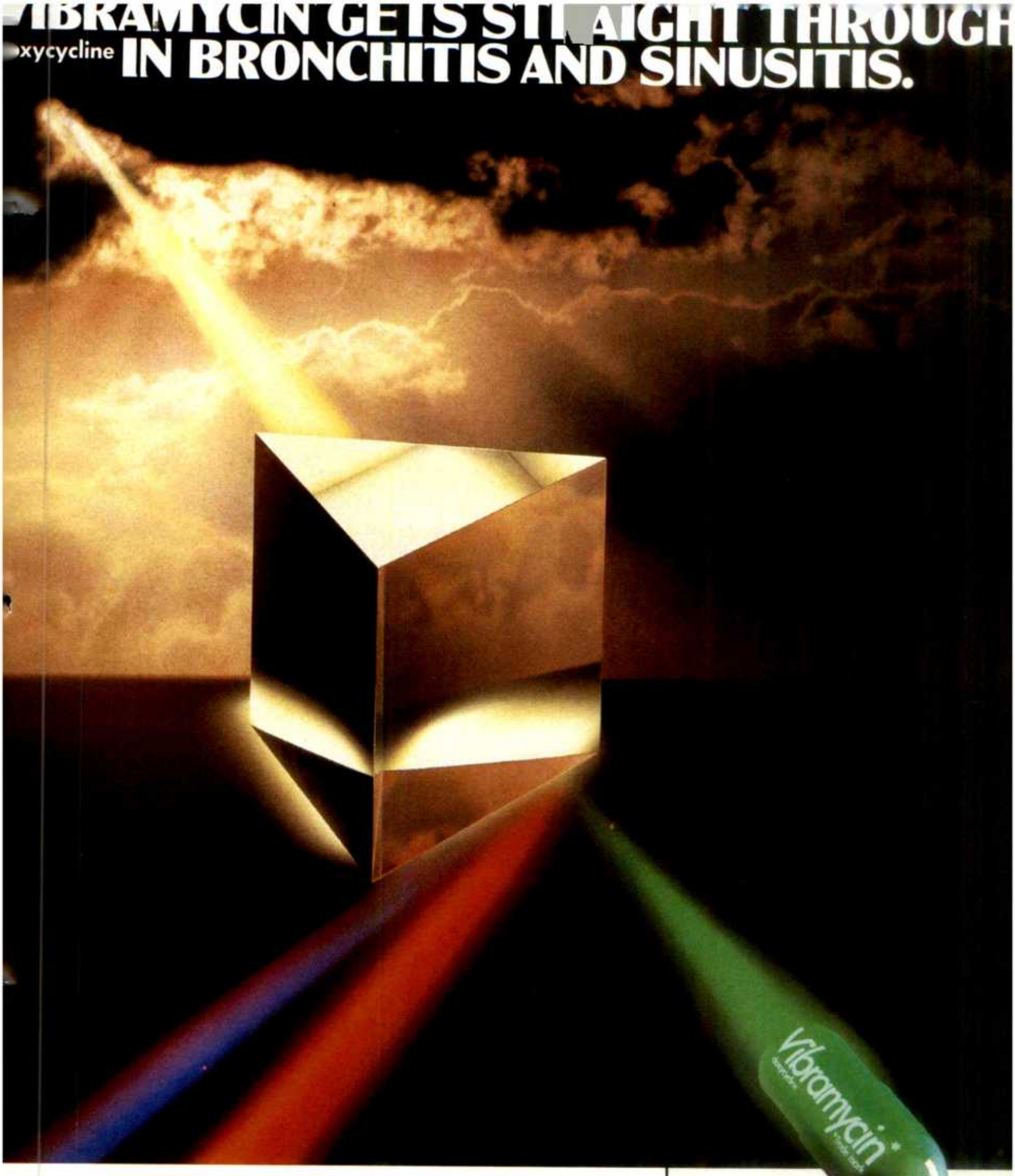
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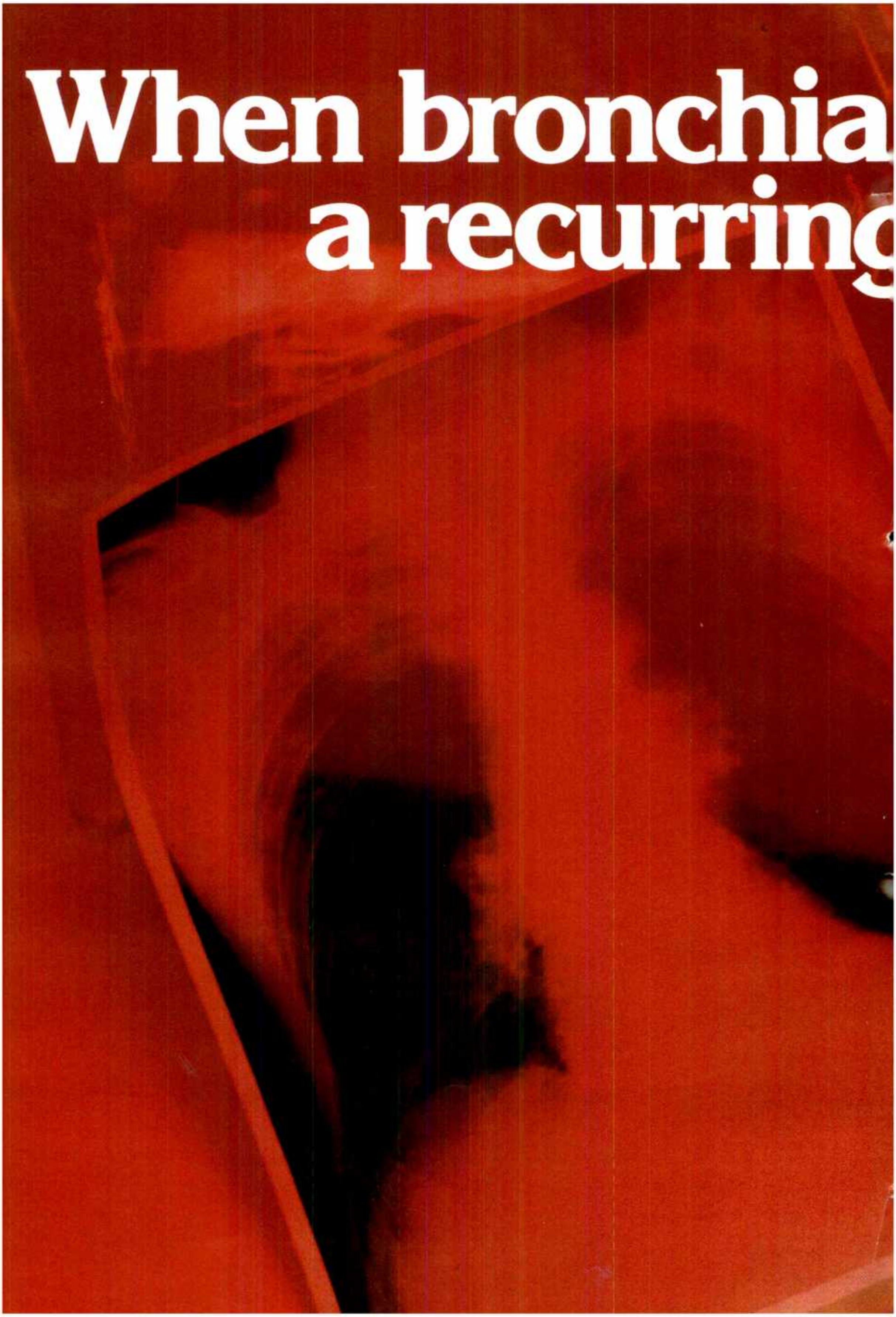
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Br. J. Dis. Chest (1982) *76*, 341

A COMPARATIVE DOUBLE-BLIND STUDY OF THE BRONCHODILATOR EFFECTS AND SIDE EFFECTS OF INHALED FENOTEROL AND TERBUTALINE ADMINISTERED IN EQUIPOTENT DOSES

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Summary

Increasing doses of fenoterol and terbutaline were administered by inhaler to 12 stable asthmatics in a double-blind crossover trial. 100 μg doses of fenoterol were shown to be equal in potency to 250 μg doses of terbutaline, as measured by increases in forced expiratory volume in the first second (FEV_1) and specific airways conductance (sGaw).

FEV_1 and sGaw remained significantly greater than pretreatment levels up to five hours after both drugs and terbutaline showed a significantly greater effect on FEV_1 than fenoterol after four hours suggesting a small but significantly longer duration of activity.

Fenoterol used at the dosage of 100 μg per puff (half the standard commercially available dose of 200 μg per puff) caused significantly more cardiac effects than terbutaline, as measured by the magnitude and duration of increases in heart rate, and the incidence of reported palpitations.

Introduction

Both terbutaline and fenoterol are highly active β-adrenergic agonists. When given by metered dose aerosol they produce rapid and sustained bronchodilatation in patients with reversible airflow obstruction (Ericksson & Lindgren 1978; Sackner & Silva 1978; Anderson et al. 1979).

The importance of using equipotent doses of inhaled β-agonists, when assessing their relative efficacy, duration of activity and incidence of side effects has been stressed (Freedman 1972; Madsen et al. 1979) and Heel et al. (1978) showed that the dosages used in past trials have varied widely, with confusing and often conflicting results.

In this study, we have established equipotent dosages of inhaled terbutaline and fenoterol, in terms of comparable increases produced in the forced expiratory volume in the first second (FEV_1) and specific airways conductance (sGaw) in stable asthmatic patients. By using a wide dose range, it has been possible to compare accurately the duration of activity and assess the side effects of terbutaline and fenoterol.

Patients and Methods

Patients

Twelve stable asthmatic patients (seven female, five male) attending the Asthma Clinic at King's College Hospital took part in the trial. The mean age was 33 years (range 18—62 years). All patients had previously shown at least a 20% increase in FEV_1 after inhaled β-agonist, and all were taking inhaled β-agonist regularly (salbutamol, eight; terbutaline, two; fenoterol, one; and orciprenaline, one). In addition seven patients were taking inhaled beclomethasone, four inhaled disodium cromoglycate, seven oral aminophylline and two oral prednisolone (5 mg and 7.5 mg daily).

The patients gave informed consent for the study, and permission was obtained from the Ethics Committee, King's College Hospital.

Procedure

The trial design was double blind with cross-over of active terbutaline and fenoterol inhalers between study days. Standard metered dose aerosols were used delivering 100 µg of fenoterol hydrobromide (WB Pharmaceuticals) per puff, or 250 µg of terbutaline sulphate (Astra Pharmaceuticals) per puff.

Before each study day the patients were asked to discontinue their usual inhaled β-agonist for the preceding 12 hours and oral aminophylline for the preceding 36 hours. Patients on oral or inhaled steroids or inhaled disodium cromoglycate were allowed to continue on these agents in unaltered doses throughout the study.

The patients attended on three days, approximately five days apart. On the first day, the patients were instructed in the routine of the study and baseline FEV_1 was measured. They were then given placebo inhalers (containing propellant only) in a cumulative dose of 7 puffs (1 + 2 + 4) puffs of both at 15 minute intervals. FEV_1 was measured after each dose, to assess whether any bronchoconstriction resulted from the inhalation of propellant mixtures.

On study days 2 and 3, the procedure was similar. Each patient was allowed to rest quietly for 30 minutes after arriving. Baseline values for FEV_1 (vitalograph), blood pressure, pulse rate, thoracic gas volume and airways resistance (Collins Whole Body Plethysmography, Warren E Collins, Inc) were measured. From the plethysmographic data, specific airways conductance (sGaw) was calculated (Dubois et al. 1956).

The patients were randomly allocated two inhalers on each of days 2 and 3. One inhaler contained either terbutaline or fenoterol, the other inhaler was a placebo containing propellant only. The allocation was double blind, and the active inhalers were crossed over between days 2 and 3 so that each patient acted as his/her own control. Patients were not studied on day 3 unless the baseline FEV_1 on that day was within 15% of baseline FEV_1 on day 2.

In the first part of the study a dose—response relationship was established in order to determine the equipotent dose of fenoterol and terbutaline. Patients took 1, 2, 4 and 8 puffs of each inhaler, active and placebo according to a previously constructed randomized code. Measurements of FEV_1 (best of three observations), heart rate and sGaw (best of three observations) were made every 15 minutes after each dose until a stable maximum response was recorded. Blood pressure was measured after the administration of the maximum dose. Cumulative dose—response curves were constructed from these data.

When a stable plateau had been reached after the maximum cumulative dose was given the patients were observed for a further five hours on each day to assess the duration of activity of each drug. Heart rate, FEV_1 and sGaw were measured every 30 minutes and blood pressure measured at the end of the study. The Student *t*-test for paired data was used to assess the significance of any differences in response to the two drugs.

FEV_1 and sGaw are expressed as mean maximum percentage increases over pretreatment values and plotted against the log cumulative dose. Heart rate is expressed as mean maximum increase in beats per minute over pretreatment values. To assess duration of activity, FEV_1 and sGaw are expressed as mean percentage of maximum response and heart rate as mean increase over pretreatment value at each point. All numerical results are expressed as mean value ± standard error of the mean (SEM).

Results

The trial was completed by all 12 patients. The first day measured the changes in FEV_1 after taking cumulative doses of both placebo inhalers containing propellant only. After a cumulative dose of 7 puffs, there was a mean fall (± SE) in FEV_1 of 3.1 ± 3.8% which was not statistically significant.

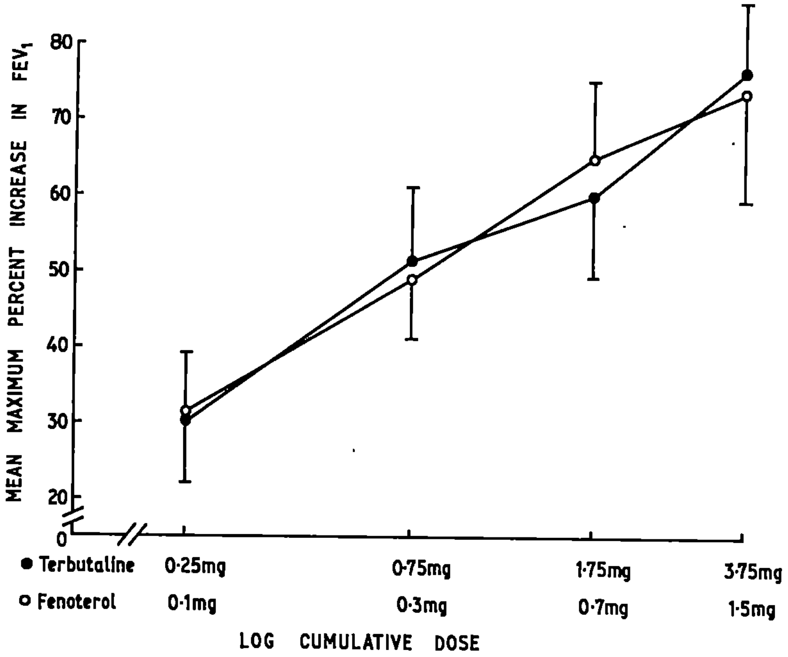

Fig. 1. Log dose–response curves, comparing increases in FEV_1 (± SE) after terbutaline with those after fenoterol. There was no significant difference in response ($P > 0.05$) between terbutaline and fenoterol at any dose level

Dose–response analysis

FEV_1. In Fig. 1 the mean maximum percentage increases in FEV_1 after fenoterol and terbutaline, are plotted against the log cumulative doses. Both drugs produced significant mean increases in FEV_1 over mean baseline values after the first dose (fenoterol 31.7 ± 6.6% $P < 0.001$, terbutaline 30.4 ± 8.4% $P < 0.005$). There were no significant differences in the mean maximum FEV_1 increases

produced after a cumulative dose of 1, 3, 7 or 15 puffs of fenoterol or terbutaline. The mean maximum peak response was not significantly different after the maximum dose of each drug; for fenoterol it was 68.7 ± 9.3% and for terbutaline 71.5 ± 11.1% ($P > 0.5$).

sGaw. In Fig. 2 the mean percentage increases in sGaw are plotted against the log cumulative doses of terbutaline and fenoterol. As with FEV_1 both agents produced significant mean maximum increases in sGaw after the first dose (fenoterol 63.4 ± 19.6% $P < 0.01$, terbutaline 65 ± 15.8% $P < 0.005$).

The responses to terbutaline and fenoterol in terms of mean maximum percentage increase in sGaw, were not significantly different at any dose levels.

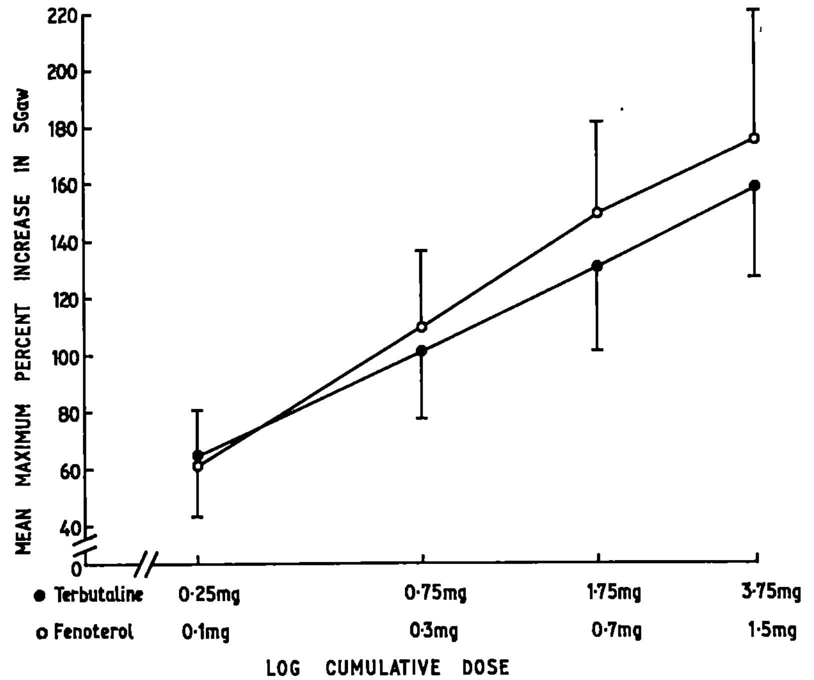

Fig. 2. Log dose–response curves, comparing increases in sGaw (± SE) after terbutaline to those after fenoterol. There was no significant difference in response ($P > 0.05$) between terbutaline and fenoterol at any dose level

Heart rate. The mean baseline values for heart rate before fenoterol was administered was 85 ± 2.4 beats per minute, and before terbutaline was administered 84 ± 2.4 beats per minute; the difference was not significant ($P > 0.5$).

The mean maximum increases in heart rate after fenoterol and terbutaline are shown in Table I. There was a small increase in mean maximum heart rate after the first dose of terbutaline (2.4 beats per minute ± 1.3 $P > 0.05$) and a significant and larger increase in mean maximum heart rate after the first dose of fenoterol (6.3 beats per minute ± 1.4 $P < 0.001$). The mean maximum increase in heart rate after fenoterol was higher at all dose levels than after terbutaline. This difference reached statistical significance after 1, 7 and 15 puffs of fenoterol compared with the equivalent of terbutaline (Table I).

Table I. Increase in heart rate following the administration of terbutaline and fenoterol

Cumulative dose fenoterol	*Mean maximum increase in heart rate (± SE) beats per minute fenoterol*	*P*	*Cumulative dose terbutaline*	*Mean maximum increase in heart rate (± SE) beats per minute terbutaline*	*P*	*Difference in mean maximum increase in heart rate (± SE) beats per minute*	*P*
0.1 mg (1 puff)	6.3 ± 1.4	< 0.001	0.25 mg (1 puff)	2.4 ± 1.3	< 0.05 NS	3.9 ± 1.3	< 0.05
0.3 mg (3 puffs)	10.8 ± 2.3	< 0.001	0.75 mg (3 puffs)	6.5 ± 1.7	< 0.005	4.3 ± 2.3	NS
0.7 mg (7 puffs)	15.3 ± 2.5	< 0.001	1.75 mg (7 puffs)	9 ± 1.7	< 0.001	6.3 ± 1.9	< 0.01
1.5 mg (15 puffs)	25 ± 3.1	< 0.001	3.75 mg (15 puffs)	15 ± 3.3	< 0.001	10 ± 3.3	< 0.02

Blood pressure. There was no significant difference from pretreatment systolic and diastolic blood pressure after taking fenoterol or terbutaline at maximum cumulative dose.

Duration of activity

The second part of the study consisted of assessing the duration of activity in terms of FEV_1, sGaw, heart rate and blood pressure of the two drugs.

FEV_1. In Fig. 3 the mean FEV_1 expressed as a percentage of maximum response is plotted against time, every 30 minutes for five hours after maximum response.

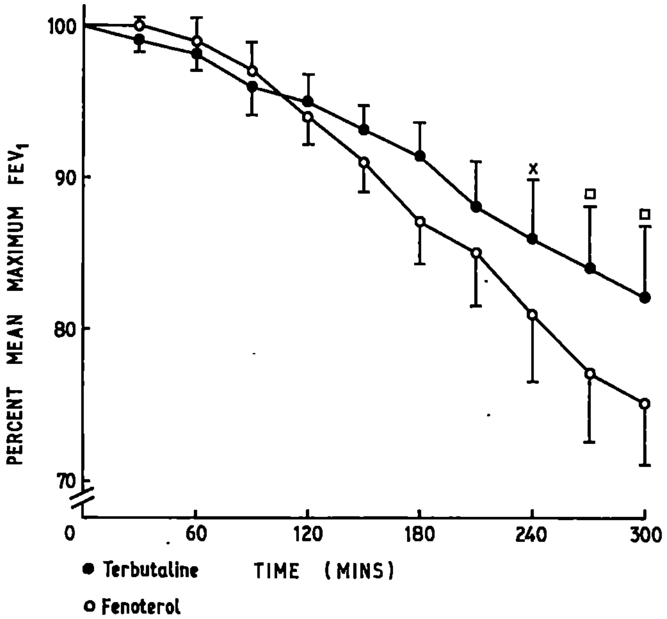

Fig. 3. Decline in FEV_1 from mean maximum value plotted every 30 minutes (±SE) for 5 hours after terbutaline and fenoterol. From 240 to 300 minutes, terbutaline had a significantly greater activity than fenoterol (×: $P < 0.01$, □: $P < 0.005$)

Values for FEV_1 declined steadily with time, for both terbutaline and fenoterol. There was no significant difference in the mean FEV_1 expressed as a percentage of maximum response until 240 minutes. At this point, the mean per cent maximum FEV_1 was significantly greater for terbutaline than for fenoterol, the mean difference being 4.5 ± 1.6% ($P < 0.01$). This trend is continued at 270 and 300 minutes, the respective differences were 7.6 ± 1.7% ($P < 0.005$) and 7.06 ± 1.9% ($P < 0.005$). Thus, the effect of terbutaline in terms of FEV_1 was significantly greater than fenoterol between 240 and 300 minutes.

sGaw. Fig. 4 shows sGaw expressed as a percentage of mean maximum response, plotted against time. sGaw shows a steady decline over the five hours of observation to 60.9 ± 3.5% of maximum sGaw for fenoterol and 66 ± 3.6% of maximum

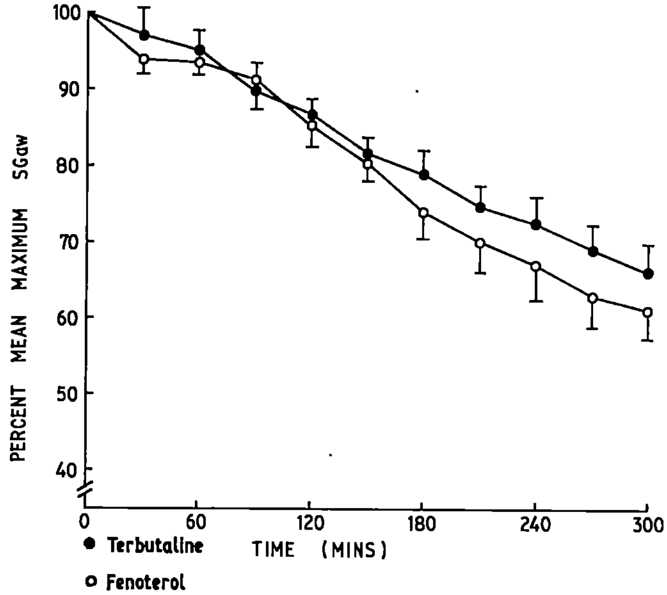

Fig. 4. Decline in sGaw from mean maximum value plotted every 30 minutes (± SE) for 5 hours after terbutaline and fenoterol. There was no significant difference between terbutaline and fenoterol at any point

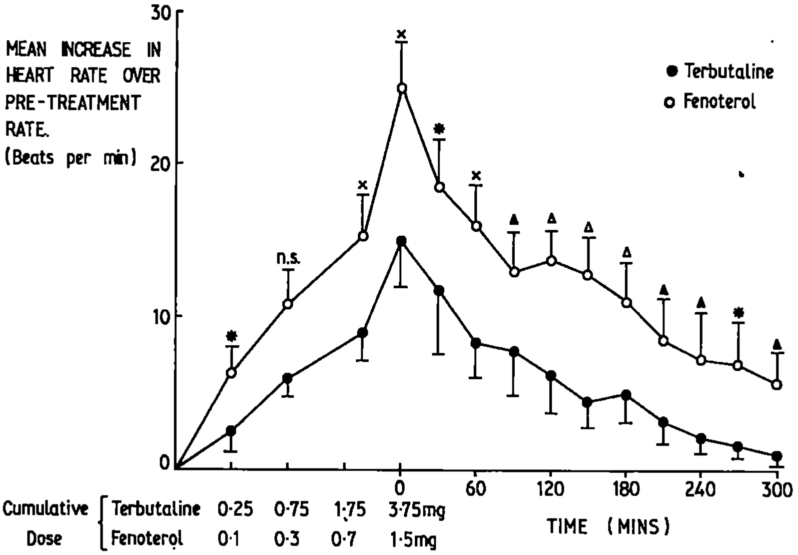

Fig. 5. The effect of terbutaline and fenoterol on heart rate (± SE). The increase in heart rate was significantly greater after fenoterol than after terbutaline at the indicated significant levels. (ns: not significant, *: $P < 0.05$, ▲: $P < 0.03$, ×: $P < 0.02$, △: $P < 0.005$

for terbutaline. There is no significant difference between the mean fall after fenoterol and the mean fall after terbutaline at any point on these curves.

Heart rate. Mean increase in heart rate is plotted against time in Fig. 5. Mean heart rate after fenoterol administration is significantly higher than after terbutaline, at each point during the five hour observation period. At 150 minutes after terbutaline the mean increase in heart rate was not significantly greater than baseline (4.8 ± 2.25 beats per min, $P > 0.05$). From 150 to 300 minutes after taking terbutaline mean heart rate was not significantly above baseline, while after taking fenoterol, mean heart rate remained significantly elevated until the end of the observation period at five hours (5.7 ± 2.1 beats per minute $P < 0.025$).

Side effects

Palpitation. Six patients complained of palpitation within 10 minutes of taking the maximum cumulative dose of fenoterol (15 puffs), and one patient who also had palpitations after fenoterol complained of palpitation after taking the equivalent dose of terbutaline. The pulse rate in all six patients complaining of palpitations was greater than 100 beats per minute (mean 118 beats/min ± 4.1 beats/min).

Tremor. Three patients developed tremor after fenoterol, two after a cumulative dose of 8 puffs and one after a cumulative dose of 15 puffs. One patient developed tremor after a cumulative dose of 15 puffs of terbutaline.

Discussion

Large and rapid increases in FEV_1 and sGaw followed the administration of the lowest dose of both terbutaline and fenoterol (Figs 1 and 2), with further increases at each dose level.

Heel et al. (1978) have reviewed the many combinations of dosages used in trials comparing fenoterol with other β-adrenergic agonists. In this trial the dose—response curves for FEV_1 and sGaw show that terbutaline in a dose of 250 μg per puff is equipotent to fenoterol 100 μg per puff.

Anderson et al. (1979) and Petit and Roberts (1973) both showed that inhaled fenoterol had a longer duration of activity than terbutaline, but these studies did not attempt to define and use equipotent doses, and with the equipotent dosages used in the present study terbutaline had a small but significantly greater duration of activity than fenoterol. Carmichael et al. (1980) also found that terbutaline given by intermittent positive pressure breathing had a significantly longer duration of activity than fenoterol given by the same method. When given over longer periods terbutaline has been shown to have a more sustained effect than fenoterol (Trembath et al. 1979).

Asthmatic patients given terbutaline by infusion and inhalation, even in relatively large doses, have few cardiovascular side effects (Thiringer & Svedmyr 1976). We have shown at all dose levels that there was a significantly smaller increase in heart rate after terbutaline than after fenoterol, even though the metered dose of fenoterol used was half the commercially available standard dose. The heart rate returned to baseline levels within two and a half hours of taking the maximum cumulative dose of terbutaline but remained significantly above pretreatment levels for the whole five hours after taking the equipotent dose of fenoterol.

Half the patients complained of palpitation after taking the maximum cumulative dosage of fenoterol, compared with one patient who had palpitations following the equipotent dose of terbutaline.

These results show significantly more cardiovascular effects from fenoterol and suggest that terbutaline has greater β_2-adrenergic receptor specificity in accord with previous pharmacological studies (Persson & Johnson 1970; O'Donnell & Wanstall 1974).

Many methods of expressing and analysing data obtained when comparing the effects of different β-adrenergic agonists on asthmatics have been proposed (Madsen et al. 1979). We have expressed our results as mean percentage changes from fixed reference points, either mean pretreatment values or mean maximum response. It is generally agreed that the expression of changes in measured indices in relative terms (such as percentage change from baseline) is preferable to the expression of results as absolute changes (Minette 1970; Kerridge 1977). However with a small degree of within-subject variation (less than 15% variation in pretreatment FEV_1 between study days in this trial) Racoveau et al. (1971) have argued that data can be accurately expressed either as absolute or relative values.

Acknowledgements

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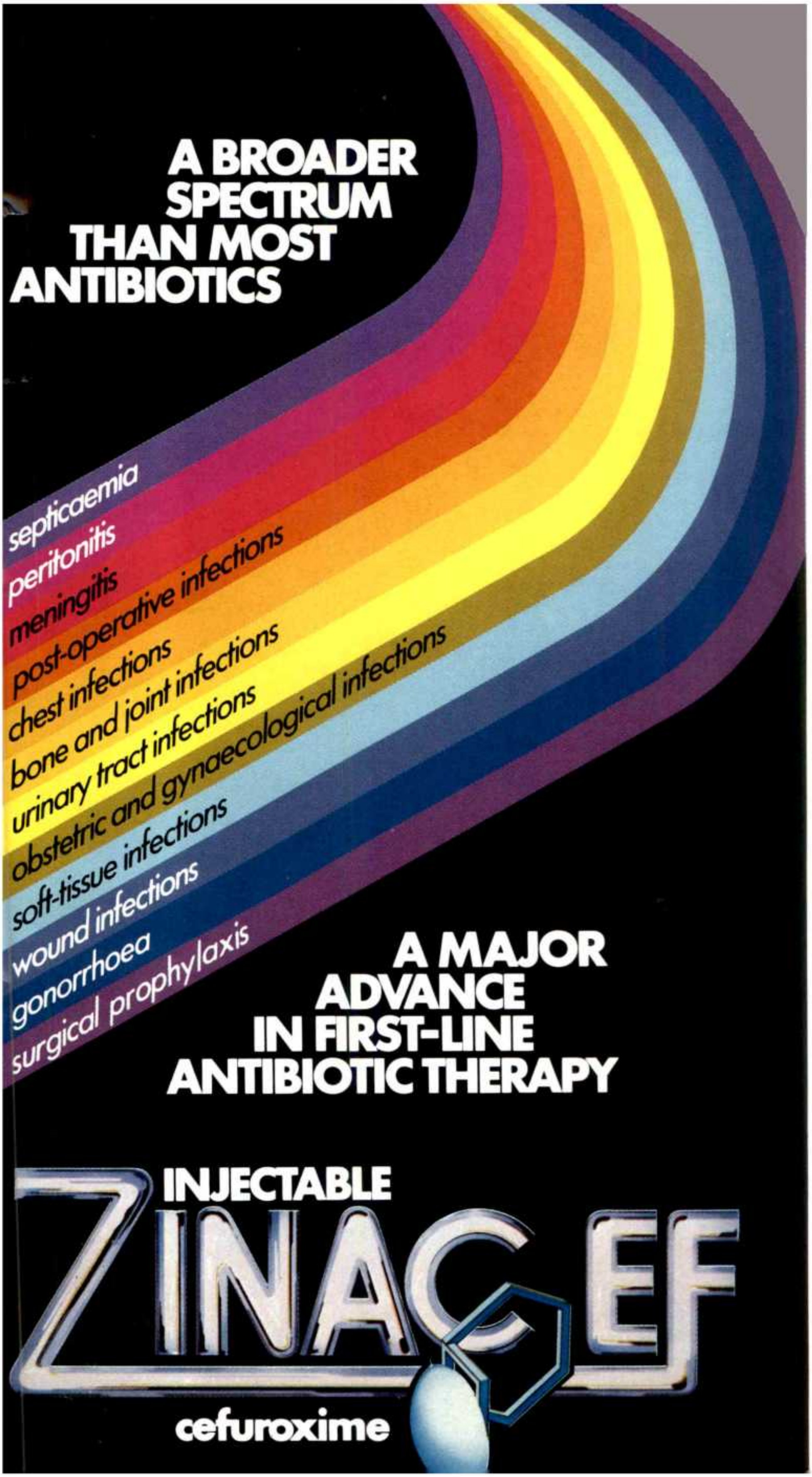
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day in three or four divided doses.
60mg/kg/day will be appropriate fo
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three divided doses.

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750mg into different sites).

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operations, may be supplemented w
two 750mg i.m. doses eight and sixt
hours later. In cardiac, pulmonary,
oesophageal and vascular operation
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of anaesthesia continuing with 750m
t.d.s. for a further 24 to 48 hours. In
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Zinacef should not be mixed in the
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Reduce dosage when renal function
markedly impaired.
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given with caution to patients recei
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experience with Zinacef has shown
this is not likely to be a problem at t
recommended dose levels.

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serum liver enzymes and transient
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the overgrowth of non-susceptible
organisms, e.g., Candida.

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5 x 750mg £14·70
1·5 gram £5·88
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infusion pack

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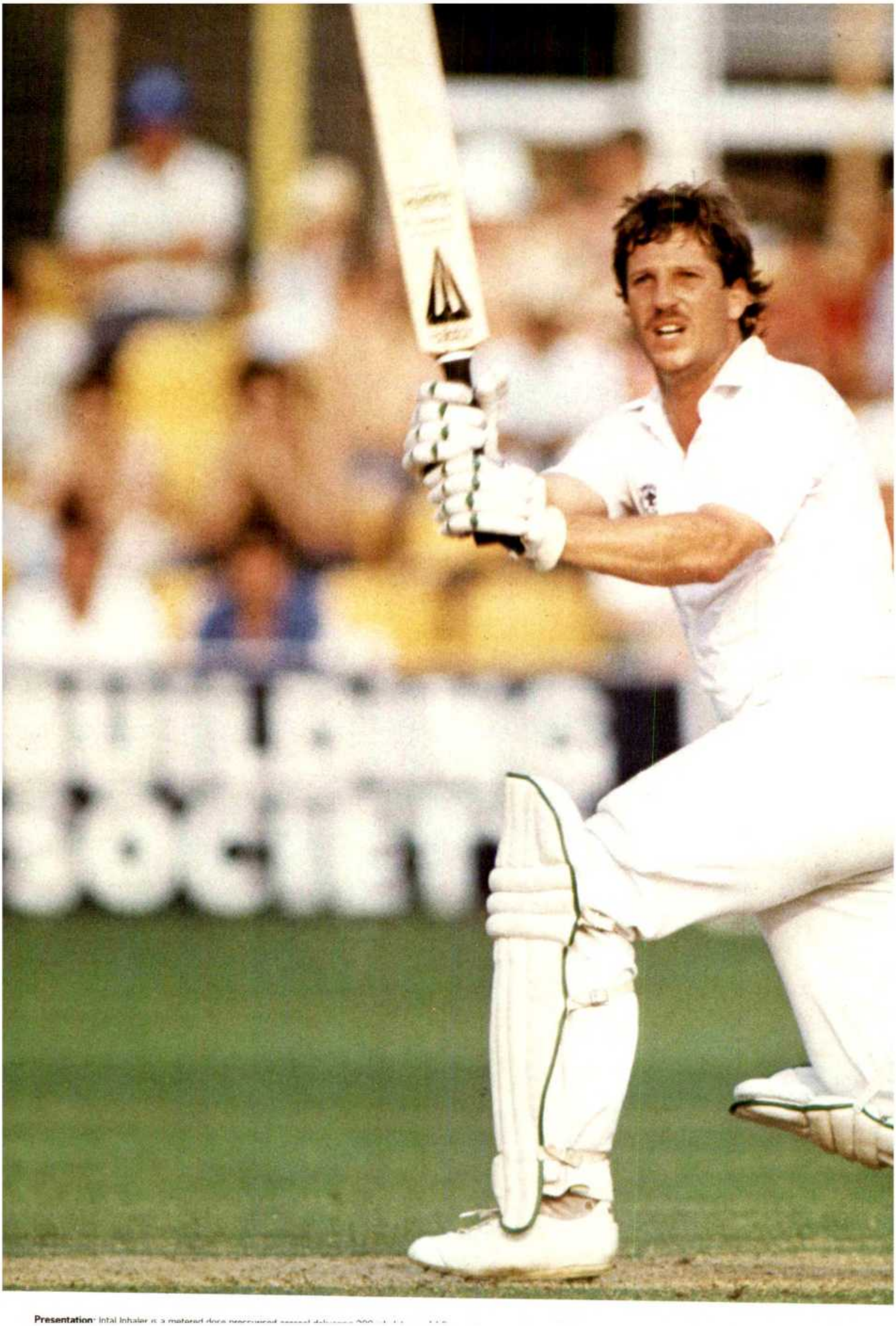

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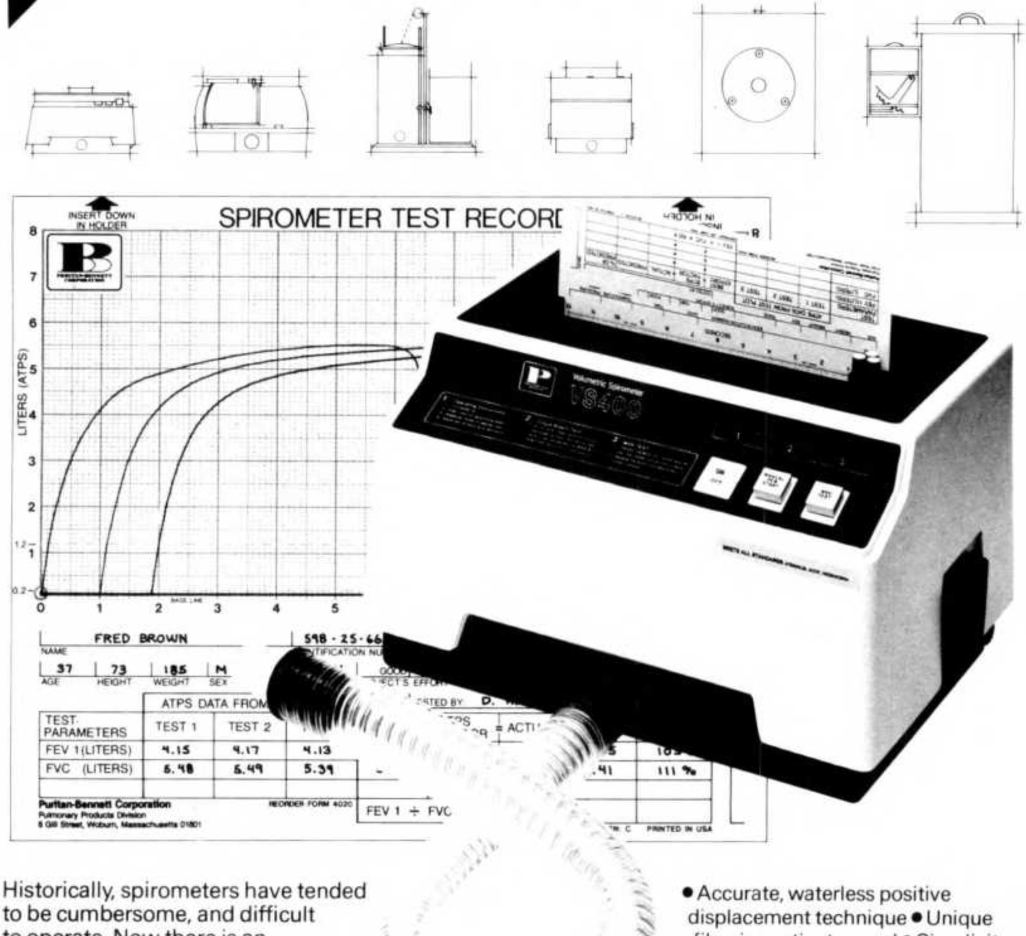

FRED BROWN
NAME
598 - 25 - 66
IDENTIFICATION NUMBER
37 AGE | 73 HEIGHT | 185 WEIGHT | M SEX
GOOD
SUBJECT'S EFFORT
TESTED BY D.

TEST PARAMETERS	TEST 1	TEST 2	
FEV 1(LITERS)	4.15	4.17	4.13
FVC (LITERS)	5.48	5.49	5.39

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Br. J. Dis. Chest (1982) *76,* 351

A COMPARISON OF THE EFFECTS OF DIFFERENT METHODS OF ADMINISTRATION OF β-2-SYMPATHOMIMETICS IN PATIENTS WITH ASTHMA

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Respiratory Laboratory, Brook Hospital, London SE18

Summary

Double-blind cross-over studies of oral and inhaled terbutaline and salbutamol have been performed in two groups of asthmatic patients. Both drugs at the doses recommended by the manufacturers produced similar maximal effects. The onset of response was faster with inhaled treatment and there was no difference in length of action between the drugs or the routes of administration. Side-effects were much more common with oral treatment. In a separate study oral and inhaled terbutaline were compared in 11 asthmatic patients and this also showed a similar maximal response in tests of forced expiration. A greater response was seen in sGaw following inhaled treatment ($P < 0.05$). These results suggest that β-2-sympathomimetic drugs should be administered by the inhaled in preference to the oral route.

Introduction

The advent of long-acting β-2-sympathomimetic drugs has provided asthmatic patients with a means of both treating and preventing acute attacks of asthma. There is controversy over the effectiveness of different routes of administration of these drugs. Inhaled therapy has a quicker onset of action, fewer side-effects, and may be better for treating exercise-induced asthma and the response to allergen challenge (Woolcock 1977). Protagonists of the oral route claim that distribution of oral drugs should be more uniform throughout the lungs with a greater effect on small airways (Larsson & Svedmyr 1977; Chopra et al. 1979; Tashkin et al. 1980).

We have compared the effects of two oral and inhaled β-2-sympathomimetic drugs, terbutaline and salbutamol, in asthmatic patients in double-blind cross-over studies. The first study was designed to investigate the relative time course of bronchodilator effect and the side-effects of the recommended doses and to compare the effects of regular aerosol, regular oral, and intermittent (symptomatic) aerosol treatment over a period of 8 weeks. The second study compared the acute effects of oral and inhaled drugs on a number of physiological tests in asthmatic patients recovering from acute exacerbations.

Patients and Methods

Two separate studies were performed.

Study 1

Sixteen asthmatic patients with at least 15% reversibility to an inhaled β-2-sympathomimetic were studied. None were taking long-term oral or inhaled corticosteroids. Each patient was studied over 8 weeks and during this period was given a terbutaline aerosol and asked to use this only in an attack of asthma. Patients were given a peak flow meter (Wright's mini peak flow meter) and a diary card and asked to record three PEF readings at the same time each morning and evening for 8 weeks. Patients were asked not to use their aerosols for at least 4 hours before recording PEF.

During the third, fourth, fifth and sixth week each patient took four different treatments (each treatment for one week).

Treatment 1 = Oral salbutamol 4 mg + aerosol placebo 8 hourly.
Treatment 2 = Oral placebo + aerosol terbutaline 500 μg 8 hourly.
Treatment 3 = Oral placebo + aerosol salbutamol 200 μg 8 hourly.
Treatment 4 = Oral terbutaline 5 mg + aerosol placebo 8 hourly.

The treatment order was randomized and the study was carried out double-blind.

At the beginnning of each of the four new treatments, and at the same time of day, patients were studied over a 5-hour period after taking the first dose of the new treatment.

The patients, who would have taken no bronchodilator treatment for 12 hours prior to the study, rested for half an hour and then recorded three forced expiratory manoeuvres into an Ohio 842 spirometer at the following times −20, −10, 0, 10 min, 30 min, 1 hr, 2 hr, 3 hr, 4 hr and 5 hr. The treatment was given at time 0. The peak expiratory flow (PEF), 1-second forced expired volume (FEV_1) forced vital capacity (FVC), and forced expiratory flow 25–75% of vital capacity (FEF_{25-75}) were the four variables taken from the forced expiratory manoeuvre. The blood pressure and pulse were recorded at each time interval with the exceptions of times −10 and + 10 min.

Study 2

Eleven asthmatic patients with at least 15% reversibility in response to an inhaled β-2-sympathomimetic were studied on two days at the same time of day. On each day, base-line measurements were made after which 5 mg terbutaline was given orally or 500 μg by metered dose inhaler together with matching placebo. The study was conducted double-blind with the order randomized.

On the oral terbutaline day another oral dose of 2.5 mg was given at 120 min and on the inhaled terbutaline day 250 μg was given at 60 min with matching placebo. Measurements were made twice before terbutaline administration and again 5, 30, 60, 120 and 180 min afterwards. Pulse and blood pressure were measured and three estimations of FEV_1, FVC, maximum flow at 50% vital capacity ($\dot{V}_{max\,50}$) using an integrated pneumotachograph; total lung capacity, residual volume and airways resistance were measured in a constant volume body plethysmograph. Airways resistance was converted to specific airways conductance (sGaw) to take account of changes in lung volume.

Results

Study 1

Table I shows the mean values of each of the four variables for the 16 patients before and after the four different treatments on the four acute study days. For

Table I. Mean PEF, FEV_1, FVC and FEF_{25-75} of the 16 patients before and after four treatments (study 1)

			−20 *min*	−10 *min*	0 *min*	10 *min*	30 *min*	1 *hr*	2 *hr*	3 *hr*	4 *hr*	5 *hr*
Oral salbutamol 4 mg	PEF	litres/min	308	315	305	319	337	340	367	368	378	364
	FEV_1	litres	1.93	1.98	1.99	2.03	2.11	2.20	2.30	2.37	2.36	2.22
	FVC	litres	2.93	2.96	2.85	3.00	3.07	3.17	3.18	3.29	3.32	3.21
	FEF_{25-75}	litres/sec	0.94	1.01	0.97	1.01	1.11	1.10	1.09	1.19	1.09	1.09
Aerosol terbutaline 500 μg	PEF	litres/min	306	320	326	377	383	385	388	385	368	363
	FEV_1	litres	2.02	2.10	2.12	2.42	2.47	2.49	2.47	2.48	2.30	2.31
	FVC	litres	2.92	2.93	3.04	3.24	3.38	3.32	3.35	3.31	3.17	3.19
	FEF_{25-75}	litres/sec	0.73	0.70	0.71	0.92	0.88	0.82	0.83	0.87	0.78	0.71
Aerosol salbutamol 200 μg	PEF	litres/min	304	312	303	371	378	380	387	384	367	354
	FEV_1	litres	1.93	1.96	2.02	2.37	2.41	2.43	2.42	2.40	2.37	2.28
	FVC	litres	2.79	2.82	2.89	3.21	3.22	3.24	3.24	3.28	3.22	3.18
	FEF_{25-75}	litres/sec	0.88	0.88	0.83	1.19	1.18	1.20	1.13	1.18	0.97	0.97
Oral terbutaline 5 mg	PEF	litres/min	315	313	319	314	332	346	364	370	360	361
	FEV_1	litres	2.05	2.05	2.10	2.08	2.19	2.29	2.41	2.52	2.34	2.37
	FVC	litres	2.97	2.98	3.00	3.03	3.12	3.10	3.22	3.38	3.17	3.22
	FEF_{25-75}	litres/sec	0.94	0.97	0.95	1.00	1.08	1.09	1.20	1.24	1.15	1.17

Table II. Percentage improvement in PEF, FEV_1, FVC and FEF_{25-75} after the four treatments.

	PEF	*FEV_1*	*FVC*	*FEF_{25-75}*
Salbutamol 4 mg tablet	26% (303)	21% (1.97)	11% (2.95)	18% (98)
Terbutaline aerosol 500 µg	24% (317)	20% (2.08)	12% (2.97)	28% (95)
Salbutamol aerosol 200 µg	30% (306)	25% (1.97)	17% (2.95)	27% (86)
Terbutaline 5 mg tablet	17% (316)	17% (2.06)	9% (2.98)	21% (95)

Note: The figures in brackets represent the mean base-line figures.

oral salbutamol and oral terbutaline (treatments 1 and 4) the maximum readings after treatment occurred between 2 and 4 hours. Aerosol terbutaline and aerosol salbutamol (treatments 2 and 3) produced maximum readings between 1 and 3 hours after treatment, but in eight patients maximum readings occurred within 30 minutes and in four of the eight within 10 minutes. The three base-line readings at −20, −10 and 0 minutes before treatment for each patient were averaged for each of the four variables on the four separate treatments. The values at 2, 3 and 4 hours after oral drugs and the values at 1, 2 and 3 hours after inhaled drugs were averaged and the response to treatment expressed as a ratio of the mean value after treatment to the mean value before treatment. The mean response to treatment expressed in this manner for each variable after each of the four drugs is shown in Table II. Individual responses of the three variables PEF, FEV_1 and FVC were expressed in the same manner. Analysis of variance of the responses, measured by these three variables, to the four treatments revealed no significant difference. The variance ratios (F value) were: PEF = 0.7, FEV_1 = 0.4, FVC = 1.2 ($V_1 = 3$, $V_2 = 60$; $F = 2.8$ for $P = 0.05$). There was no significant change in blood pressure or pulse during any of the four treatments.

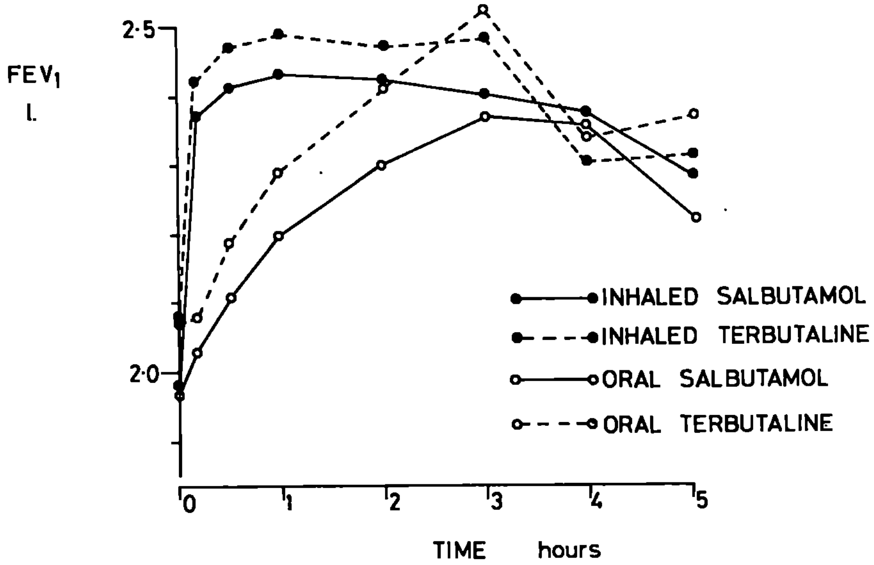

Fig. 1. Mean change in FEV_1 after the four treatments.

Table III. Mean peak flow during the weeks on five different treatments

	Litres/min
Salbutamol tablets	323
Terbutaline aerosol	305
Salbutamol aerosol	305
Terbutaline tablets	317
Intermittent (symptomatic) terbutaline aerosol	295

Tremor was noted in four and headaches in one patient following oral salbutamol, palpitations in two patients following aerosol terbutaline, lightheadedness in one patient after aerosol salbutamol, and tremor in nine and palpitations in one patient after oral terbutaline.

The most striking difference between the four treatments was the time course of response. In Fig. 1 the mean change in FEV_1 is shown for the four treatments. It can be seen that the onset of response is much more rapid with the aerosol than the oral route. The maximum effect was similar for all four treatments and occurred at 1 hour after aerosol and 3 hours after oral drugs.

The mean peak flow during the weeks on the five different treatments is shown in Table III. Analysis of variance revealed no statistical difference between any of these means though the regular bronchodilator treatment means are all higher than the mean during intermittent (symptomatic) terbutaline aerosol, and the regular 'oral' means were both higher than the 'aerosol' means (variance ratio = 0.24; $V_1 = 4$, $V_2 = 75$, $F = 2.5$ for $P = 0.05$).

Study 2

Table IV shows the values for FEV_1, FVC, $V_{max\ 50}$ and sGaw for inhaled and oral terbutaline. Again the maximum response was similar for the two methods of administration when assessed by response of FEV_1, FVC and $V_{max\ 50}$ and these responses occurred at 1 hour and 3 hours after the first dose of inhaled and oral treatment respectively. Although the increase in FEV_1 was slightly greater after

Table IV. Mean FEV_1, FVC, $V_{max\ 50}$, sGaw and RV before and after oral and inhaled terbutaline (study 2)

Minutes after terbutaline	*FEV_1* (litres)		*FVC* (litres)		*$V_{max\ 50}$* (litres/sec)		*sGaw* (kPa/litre/sec)		*RV* (litres)	
	Oral	*Inhaled*	*Oral*	*Inhaled*	*Oral*	*Inhaled*	*Oral*	*Inhaled*	*Oral*	*Inhaled*
Base-line	1.85	1.90	2.72	2.77	1.63	1.79	0.47	0.49	4.96	4.61
5	1.89	2.18	2.80	2.95	1.70	2.17	0.54	0.82	4.51	4.23
30	1.96	2.24	2.96	3.08	1.78	2.21	0.58	0.76	3.95	4.11
60	2.09	2.29	3.00	3.10	1.95	2.21	0.69	0.85	3.86	4.36
120	2.18	2.31	3.16	3.12	2.04	2.15	0.69	0.95	4.00	4.27
180	2.19	2.29	3.15	3.09	2.09	2.24	0.84	0.87	3.88	4.10

inhaled than oral terbutaline and the increase in FVC slightly greater after oral than inhaled terbutaline, these differences were not statistically significant. Increases in sGaw were significantly greater (paired *t*-test $P < 0.05$) after inhaled than oral terbutaline. Of the four variables measured only sGaw was further increased after a second dose of oral or inhaled terbutaline.

Inhaled terbutaline produced a small decrease in pulse rate while with oral terbutaline there was a small increase. The changes after the two treatments were significantly different at 60 min (paired *t*-test $P < 0.05$). There were no significant changes in blood pressure on either treatment.

Discussion

Few direct comparisons between inhaled and oral β-2-sympathomimetic treatment have been reported. In this study the onset of action was again shown to be much more rapid with inhaled drugs than oral drugs and this is a well recognized advantage of inhaled treatment. The maximum bronchodilation in both studies was the same for each route of administration at doses recommended for routine use.

The duration of action of oral and inhaled drugs has not been previously compared on the same group of patients. Significant bronchodilation for up to 7 hours after inhaled salbutamol and/or terbutaline has been noted (Choo-Kang et al. 1973) and after oral salbutamol and terbutaline the duration of action varies from 5 to 8 hours (Legge et al. 1971; Cochrane et al. 1973; Berg 1975). Our results suggest that there is no significant difference between oral and inhaled routes in the rate of fall of FEV_1 between 3 and 5 hours. With the more rapid onset of action following aerosol, the total area under the therapeutic 'curve' is therefore greater with aerosol treatment.

In the first study there was no significant acute change in blood pressure or pulse after any of the four treatments which is in agreement with some previous studies (Thiringer & Svedmyr 1976; Sackner & Silva 1978) but in the second study oral terbutaline produced a significant increase in pulse rate. In the first study side-effects were much more common after oral than aerosol treatment and there were twice as many side-effects with oral terbutaline compared to oral salbutamol.

Since sGaw is particularly dependent on the characteristics of the upper airways and FVC may reflect overall airway function more than FEV_1, the greater effect on sGaw with inhaled therapy and the relative effects on FEV_1 and FVC in the second study lend some support to the suggestion that inhaled drugs exert a greater effect on large airways (Larsson & Svedmyr 1977; Chopra et al. 1979; Tashkin et al. 1980). Only sGaw increased significantly after extra doses of both inhaled and oral therapy whereas FEV_1, FVC and V_{max50} did not, which is in agreement with previous work (Sackner & Silva 1978).

In conclusion we have shown that aerosol therapy has many advantages over oral therapy including rapid onset, a greater total duration of action, similar peak effect, and fewer side-effects. The clinical relevance of the possible greater overall effect on the airways with oral drugs needs further investigation.

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THE DIAGNOSTIC VALUE OF ROUTINE CULTURE OF BRONCHIAL WASHINGS IN TUBERCULOSIS

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Summary

Fibreoptic bronchoscopy was done in 164 patients with clinical and radiographic features which suggested non-tuberculous chest disease. Bronchial washings collected during the procedure were examined for acid-fast bacilli by smear and culture. The smear was positive in 15 patients and cultures were positive in 23 patients. We suggest that in regions of high tuberculosis prevalence bronchial washings should be examined routinely for tubercle bacilli.

Introduction

Although the role of fibreoptic bronchoscopy in the diagnosis of smear-negative pulmonary tuberculosis has been established (Damek & Bower 1979; Sarkar et al. 1980) it is not clear whether routine smear and culture examination of bronchial washings are helpful in diagnosing occult pulmonary tuberculosis. Kvale et al. (1979) have not found it useful in the United States but, this observation may not be true in countries like India, where prevalence of tuberculosis is considerably higher.

It is the purpose of the present study to analyse our practice of routine smear examination and culture of bronchial washings for *Mycobacterium tuberculosis*. The study comprises 164 bronchial washings collected during fibreoptic bronchoscopy done at the Hospital for Chest Diseases and Tuberculosis, Jaipur, India during 1978–80. The pre-bronchoscopy sputum smear for acid-fast bacilli (by a concentration method) was negative in all these patients. The clinical and radiological features were in favour of non-tuberculous pulmonary disease rather than tuberculosis and some of these patients had normal chest radiographs with haemoptysis as the only symptom.

Materials and Methods

Bronchial washings were collected in a trap bottle included in the suction line, in all patients. 10–15 ml of sterile normal saline was used for bronchial toilet when required. An aliquot of the sample was used to prepare a smear by a concentration method and was examined for acid-fast bacilli after staining with the Ziehl-Neelsen method. The other part of the sample was cultured on Lowenstein Jensen media for tubercle bacilli.

Lidocaine (2%) was used for local anaesthesia (5–7 ml in each case).

Results

The radiological features of 164 patients who underwent fibreoptic bronchoscopy are shown in Table I. The bronchoscopic abnormalities seen in these patients included ulceration in eight and hyperaemia with oedema in 15.

Fifteen out of 164 bronchial washings were positive for acid-fast bacilli by smear examination. In all of these and another eight cases the culture was positive for *M. tuberculosis* after six weeks. Non-tuberculous mycobacteria were not isolated from any of our cases.

Antituberculosis chemotherapy was started in 15 patients with positive bronchial aspirate smear for acid-fast bacilli, and in the other eight patients the treatment was started after the positive culture was obtained. After 3 months the clinical and radiological response was good in all patients.

Table I. Radiological features of patients undergoing bronchoscopy

Type of lesion	*No. of patients*	*Positive for* Mycobacterium
Collapse consolidation	39	2
Consolidation lower zone	37	3
Consolidation with cavity lower zone	27	8
Heterogeneous shadows lower zone	27	5
Parahilar shadows	7	2
Solitary nodule	3	—
Normal chest radiograph with haemoptysis	24	3
Total	164	23

Discussion

Kvale et al. (1979) advised against routine culture of bronchial washings for *M. tuberculosis* in the United States as the policy is not effective on cost–benefit analysis. Our experience in India of routine screening of bronchial washings for tubercle bacilli was different and the policy has been very useful in diagnosis of pulmonary tuberculosis in patients where clinical and radiological features were in favour of non-tuberculous pulmonary disease. Without routine examination of bronchial aspirate the diagnosis in our patients would have been delayed or missed.

Conte and Laforet (1962), Bartlett et al. (1976) and Fossieck et al. (1977) have reported that culture of bronchial aspirates gives false negative results due to the inhibitory effect of local anaesthetic on growth of *M. tuberculosis*. The amount of lidocaine was kept to a minimum in our study so as to get the maximum yield of positive cultures. Positive cultures in all the patients in whom smear for acid-fast bacilli was positive (15) suggests that the inhibitory effect of lidocaine cannot be great. The good clinical and radiological response after 3 months of anti-tuberculosis chemotherapy makes false positive results due to laboratory error very unlikely.

In our experience in India, routine examination of bronchial washings for *M. tuberculosis* is advisable irrespective of the clinical and radiological status of patients undergoing fibreoptic bronchoscopy.

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PULMONARY ASPERGILLOMA AFTER RADIATION THERAPY

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Summary

Two patients with pulmonary aspergilloma in areas of lung which had received radiotherapy are described. This association is uncommon and it is suggested that they arose in fibrotic lung caused by the radiation therapy.

Introduction

Aspergillomas usually appear within sterile cavities associated with chronic lung damage. Colonization occurs most commonly in residual tuberculous cavities but fungus balls also develop in pneumoconiosis, bronchial carcinoma and lung fibrosis associated with ankylosing spondylitis and idiopathic lung fibrosis (Barkey & Rose 1976).

We describe two cases of pulmonary aspergilloma following radiation therapy.

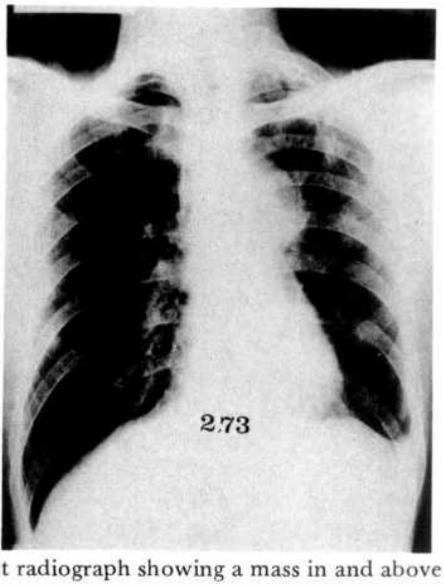

Fig. 1. Chest radiograph showing a mass in and above left hilum

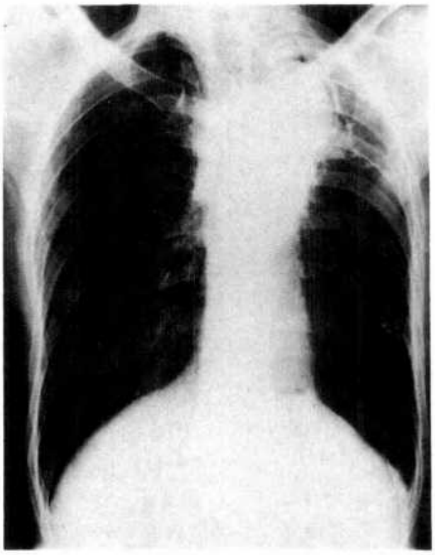

Fig. 2. Chest radiograph with a large aspergilloma at the left apex

Case Studies

Case 1

A 44-year-old man developed tightness in the chest in January 1973. A chest radiograph showed a mass in and above the left hilum and some linear shadowing in the periphery of the left upper lobe (Fig. 1). Bronchoscopy revealed some distortion of the trachea only. He was given a 19-day course of radiotherapy to a total of 4275 rads to the affected area. He became symptom free and the chest radiograph in May 1973 showed only a little peripheral linear

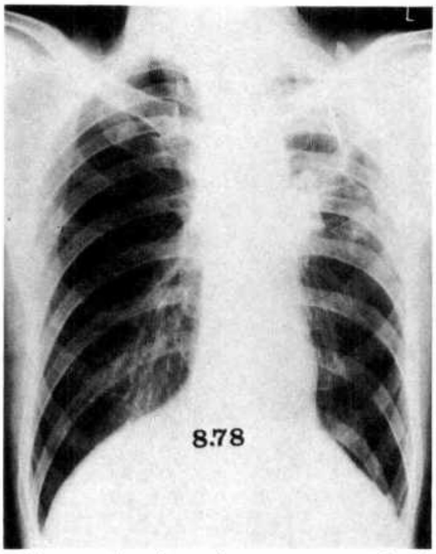

Fig. 3. Chest radiograph now showing a large empty cavity in the left upper lobe

shadow in the left upper lobe. By September 1974 there was more fibrosis in the left upper lobe and traction on the trachea. There was no evidence of recurrence of the tumour. A further radiograph in 1977 (Fig. 2) showed several small cavities and one large cavity containing a fungus ball at the left apex. The serum precipitin test with *Aspergillus fumigatus* extract was strongly positive. The chest radiograph in 1978 showed an empty cavity (Fig. 3). He remains well and symptom free, and the aspergilloma has not recurred.

Case 2

A 45-year-old woman had a right mastectomy for cancer in June 1972 followed by a 19-day course of radiotherapy to a total dose of 4000 rads. She was well until September 1977 when she developed pain and weakness in the right arm. There were enlarged lymph nodes in the right axilla and above the clavicle. She had a 10-day course of 3000 rads to the supraclavicular nodes, followed after one month by a 22-day course of 5000 rads to the axilla. The pain was relieved but she was left with a weak swollen arm. The chest radiograph, which was normal in 1974, showed the development of a little linear shadowing in the right upper zone by August 1977. It was repeated in 1979 because she had a chronic cough and showed a large cavity in the right upper lobe containing a fungus ball (Fig. 4) which was confirmed by tomography. The humeral head and the third and fourth ribs showed radiation necrosis. Aspergillus precipitins were strongly positive. She died from carcinomatosis in 1980 but postmortem examination was not done.

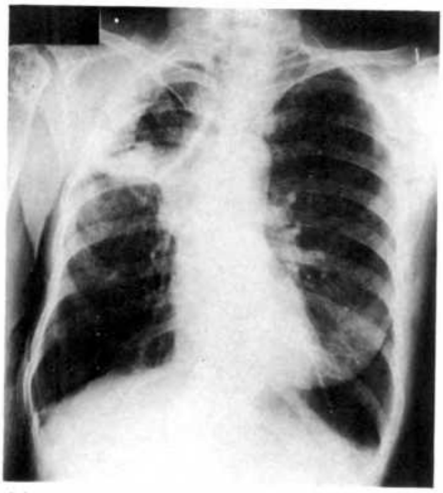

Fig. 4. Chest radiograph with a large cavity in the right upper lobe containing an aspergilloma

Discussion

The pulmonary effects of radiation therapy have been divided into two phases (Gross 1977). The first phase, consisting of a pneumonitis occurring a few weeks after irradiation, is followed by fibrosis which is usually well established a year after therapy. In our cases cystic areas in the fibrotic lung, presumably occurring after radiotherapy, became colonized by fungus. This often occurs as a complication of other fibrotic lung conditions (Davies 1970) but it is unusual following radiation therapy, only two cases being recently reported (Long et al. 1981).

In our first patient the mass in the left hilum was not proven to be a carcinoma. The tracheal distortion and the tomographic appearances suggest that it was not at that stage a mycetoma and it disappeared with radiotherapy. The aspergilloma which developed four years later disappeared spontaneously and this occurs in about 10% of cases (British Thoracic and Tuberculosis Association 1970). In both cases the radiological features were typical of aspergilloma and precipitin tests were positive.

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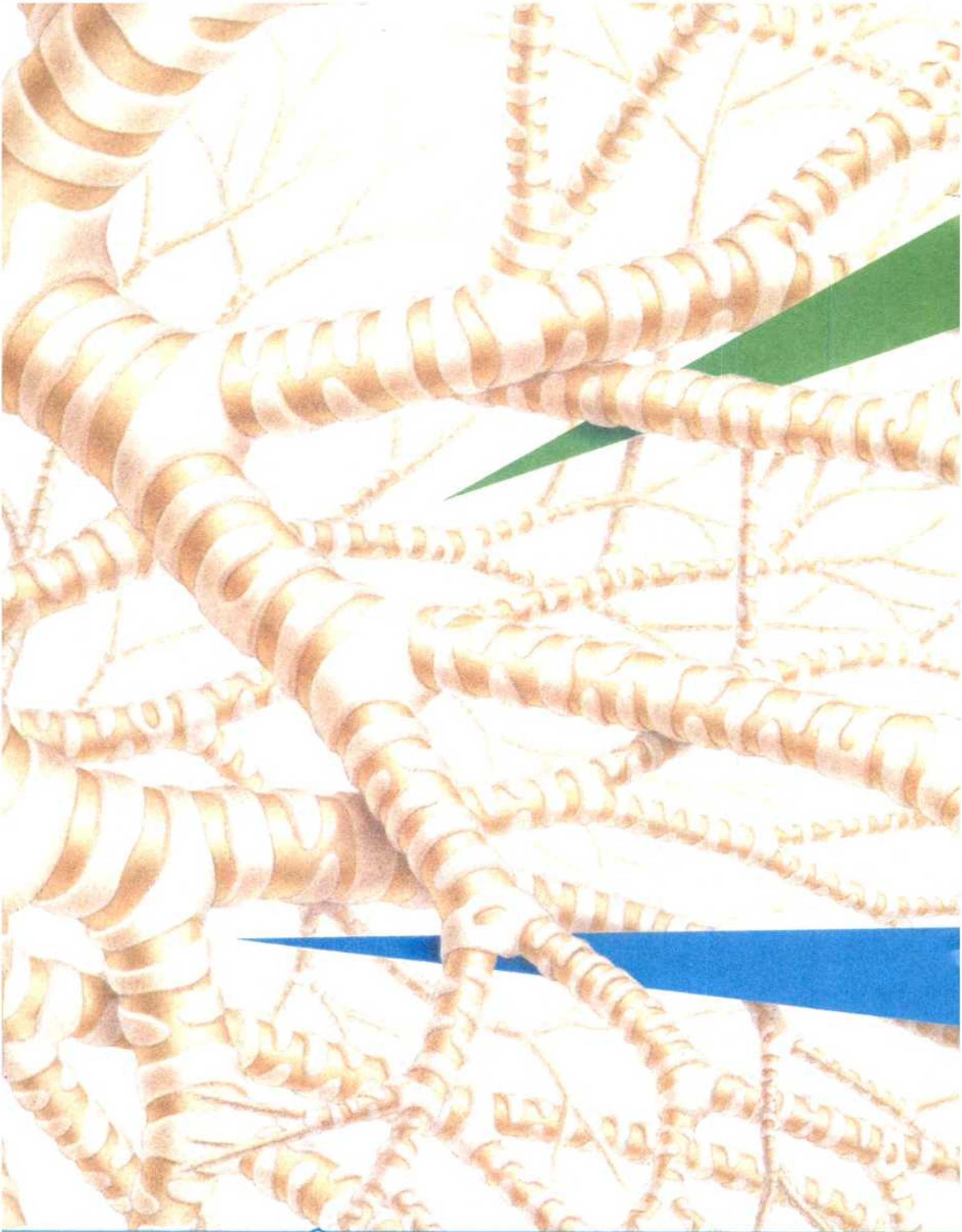

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MOUTH SPRAYING VERSUS INHALATION OF FENOTEROL AEROSOL IN HEALTHY SUBJECTS AND ASTHMATIC PATIENTS

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Summary

Four hundred μg of fenoterol aerosol were administered to 10 healthy subjects and nine asthmatic patients. Fenoterol was either inhaled or sprayed into the mouth carefully avoiding inhalation. Forced vital capacity (FVC), forced expiratory volume in one second ($FEV_{1.0}$), maximal expiratory flow rates (MEFR), specific airways conductance (sGaw), total lung capacity (TLC), residual volume (RV), and heart rate (HR) were measured before and up to one hour after fenoterol administration. FVC, $FEV_{1.0}$, MEFR and sGaw increased significantly after inhalation of fenoterol in both asthmatic patients and healthy subjects. The increase was significantly greater in the asthmatic group. After buccal administration of fenoterol FVC, $FEV_{1.0}$ and sGaw increased significantly in both asthmatic patients and healthy subjects, and there was no significant difference between the two groups. Increased heart rate and side effects were observed only in healthy subjects and only after inhalation. Buccal administration of fenoterol to both asthmatic patients and healthy subjects induced a clearcut bronchodilation (though less than that produced by inhalation), probably by absorption of the drug through the oral mucosa.

Introduction

In recent years dose–response curves, pharmacokinetics, routes of administration, bronchodilation and side effects of β_2-agonists have been extensively studied both in normal subjects and in patients with bronchial asthma and chronic obstructive lung disease (Paterson et al. 1979). With minor differences all the β_2-stimulants show a definite bronchodilating action, which is generally dose dependent up to a maximum level (Larsson & Svedmyr 1977). Side effects depend on dose and route of administration (Thiringer & Svedmyr 1976). Chronic therapy is associated with a reduction of side effects without affecting the bronchodilating effects of these drugs (Svedmyr et al. 1974). It is generally accepted that the inhalation route offers the most rapid bronchodilating effect and fewer side effects with lower doses (Williams & Kane 1975). After inhalation there is significant bronchodilation at a time when no detectable blood level of the drug can be found. This is a strong argument for a local action in the lung (Paterson et al. 1979).

There is strong evidence that only a small percentage of an inhaled dose reaches the lung, the rest being swallowed or remaining in the mouth and pharynx (Blackwell et al. 1974). This raises the question whether β_2-agonists, in aerosol form, may be absorbed through the buccal mucosa and act systemically, i.e. through the blood stream. Davies (1975) has dismissed this possibility since he found no increase in heart rate after nebulization of isoproterenol into the mouth. However, Minette and Brunix (1967) have shown in coal miners that inhaled isoproterenol induced a definite bronchodilation without changes in heart rate. Recently Shore and co-workers (1976) have reported in asthmatic children that fenoterol delivered directly into the mouth from a pressurized canister produced a significant increase in peak expiratory flow rate (PEFR) and in forced expiratory volume in one second ($FEV_{1.0}$). However, no precautions were taken to avoid inhalation of the product.

This study was designed to obtain further information on the possibility that a β_2-agonist may be absorbed through the oral mucosa and act on the bronchial β_2-receptors via the blood stream.

Materials and Methods

Ten normal subjects (four women; mean age of the group 27.7 years; range 17–40 years) and nine asthmatic (American Thoracic Society 1962) patients (one women; mean age of the group 45.9 years; range 23–68 years) were studied on two consecutive days. All had volunteered for the study and had given informed consent. Asthmatic patients were known to show at least 15% improvement in their $FEV_{1.0}$, after inhalation of 200 μg of fenoterol. The subjects received 2 successive puffs of fenoterol (200 μg per puff) either by inhalation at the beginning of a slow maximal inspiration followed by 10 seconds' breath holding, or by spraying the drug into the mouth. To avoid inhalation., subjects inspired with the canister between the lips up to total lung capacity (TLC), and the dose was then delivered into the mouth while the breath was held for 10 seconds. Thereafter, they slowly expired through the nose to the end-tidal level. Finally, the canister was withdrawn while the subjects expired maximally through the mouth in order to avoid inhalation of any drug remaining in the mouth in aerosol form. The procedure had been practised by each subject using a placebo canister until a correct manoeuvre was obtained.

We measured forced vital capacity (FVC), $FEV_{1.0}$, TLC, residual volume (RV), specific airway conductance (sGaw), maximal expiratory flow rates (MEFR) and heart rate (HR). Specific airway conductance (the reciprocal of airway resistance divided by the thoracic gas volume) was measured with a pressure-corrected flow body plethysmography (Stănescu et al. 1972). The mean value of four measurements of sGaw is reported. TLC was calculated as the sum of the inspiratory capacity and thoracic gas volume. The highest of three TLC values is reported. Maximal expiratory flow rates, FVC and $FEV_{1.0}$ were obtained from three forced expirations. Flow rate was measured with a Fleisch pneumotachograph and lung volume was obtained from electronic integration of the flow signal. Flow rate and volume were respectively displayed on the y and x axis of a storage oscilloscope to get MEFR. Peak expiratory flow rate (PEFR) and maximum flows at 50 and 75% of expired FVC (MEF_{50} and MEF_{75}) were measured from photographs. Lung volume was simultaneously recorded against time to obtain FVC and $FEV_{1.0}$. Heart rate was measured for 60 seconds after five minutes' rest. Tremor and palpitations were assessed by questioning the subjects.

Measurements were made before and 5, 30 and 60 minutes after fenoterol administration. Subjects were randomly allocated to one of the two routes of administration the first day, the other route being tested the following day. The experiment started each day at 9 a.m.

Asthmatic patients had stopped their bronchodilator therapy, which included in each case β_2-agonists, since the previous evening. Beclomethasone dipropionate, when administered, was continued at the same dose.

Results, expressed in absolute values, were compared for each day and for the buccal *v.* inhalation routes with the paired *t*-test, each subject acting as his own control. Asthmatic patients and normal subjects were compared using the non-paired *t*-test and expressing the results as changes in percentage of the initial values. Significance level was fixed at the 5% level.

Results

Normal subjects

No significant differences were seen between any of the pretreatment values on both days. *After inhalation of fenoterol* mean values of FVC, $FEV_{1.0}$, $FEV_{1.0}$/FVC, sGaw and MEF_{50} were significantly higher than pretreatment values within five minutes (Table I). A further increase occurred during the following hour, the maximum being reached after 30 or 60 minutes. TLC and RV did not change significantly. Heart rate increased at five and 30 minutes, though not significantly (Fig. 1).

Table I. Mean values (and standard deviation) of lung function tests and heart rate before and after *inhalation* of 400 μg fenoterol in normal subjects and asthmatic patients

	Normal subjects				*Asthmatic patients*			
	Before	*After fenoterol*			*Before*	*After fenoterol*		
		5 min	*30 min*	*60 min*		*5 min*	*30 min*	*60 min*
FVC (l)	5.23	5.39*	5.42*	5.43*	3.59	4.21*	4.27*	4.22*
	(0.96)	(1.00)	(0.99)	(1.05)	(1.46)	(1.49)	(1.54)	(1.51)
$FEV_{1.0}$ (l)	3.97	4.26*	4.27*	4.31*	1.92	2.43*	2.52*	2.49*
	(0.75)	(0.80)	(0.79)	(0.87)	(1.03)	(1.27)	(1.33)	(1.30)
RV (l)	1.83	1.74	1.73	1.73	4.14	3.21*	3.20*	3.26*
	(0.53)	(0.43)	(0.52)	(0.35)	(1.17)	(0.96)	(0.90)	(1.06)
sGaw ($kPa^{-1}.sec^{-1}$)	2.10	3.74*	3.95*	3.75*	0.65	1.29*	1.38*	1.48*
	(0.56)	(1.44)	(1.20)	(1.13)	(0.37)	(0.96)	(1.03)	(1.07)
MEF_{50} ($l.sec^{-1}$)	3.82	4.62*	4.69*	4.64*	1.16	1.74*	1.77*	1.83*
	(0.93)	(0.94)	(0.98)	(1.47)	(0.89)	(1.38)	(1.33)	(1.36)
HR ($beats.min^{-1}$)	78.80	85.10	83	80.2	92.9	91.6	91.2	90.11
	(7.07)	(10.16)	(8.50)	(6)	(21.2)	(21.7)	(18)	(17.6)

* Significantly different from control value ($P < 0.05$).

For the sake of brevity results of TLC, PEFR and MEF_{75} were omitted from the tables.

After buccal administration, changes followed a similar time course and mean values of FVC, $FEV_{1.0}$, RV and MEF_{75} were significantly different from pretreatment values within five minutes (Table II). There was a further significant increase in FVC, $FEV_{1.0}$ and MEF_{75} 60 minutes later (Fig. 2). Specific airway conductance also increased significantly after both 30 and 60 minutes (Fig. 2). The decrease of heart rate was not statistically significant (Fig. 1). Although the

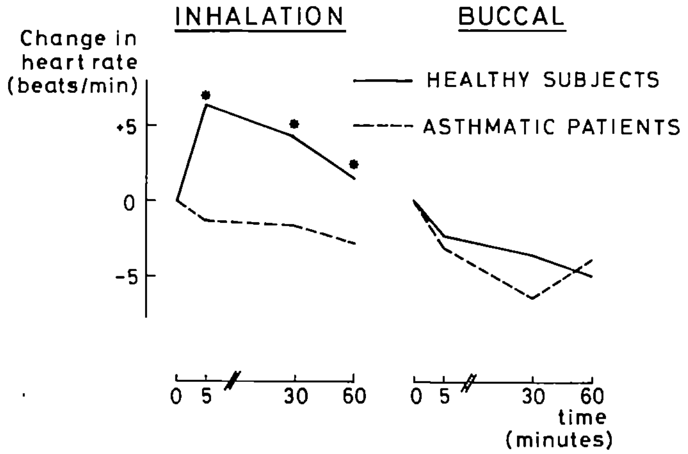

Fig. 1. Change of heart rate after inhalation or buccal spraying of fenoterol in healthy subjects and asthmatic patients. Asterisks show significant differences ($P < 0.05$) between routes of administration in healthy subjects

Table II. Mean values (and standard deviation) of lung function tests and heart rate before and after *buccal administration* of 400 μg fenoterol in normal subjects and asthmatic patients

	Normal subjects				*Asthmatic patients*			
	Before	*After fenoterol*			*Before*	*After fenoterol*		
		5 min	*30 min*	*60 min*		*5 min*	*30 min*	*60 min*
FVC (l)	5.18	5.37*	5.40*	5.41*	3.71	3.94*	4.02*	4.02*
	(0.96)	(0.99)	(1.01)	(1.02)	(1.54)	(1.53)	(1.52)	(1.43)
$FEV_{1.0}$ (l)	4.02	4.15*	4.21*	4.24*	1.93	2.00	2.10*	2.13*
	(0.78)	(0.78)	(0.80)	(0.80)	(0.99)	(0.96)	(1.03)	(1.06)
RV (l)	1.86	1.58*	1.56*	1.68	4.30	3.77	3.74*	3.66*
	(0.55)	(0.46)	(0.48)	(0.45)	(1.39)	(1.16)	(1.41)	(1.40)
sGaw ($kPa^{-1}.sec^{-1}$)	2.11	2.33	3.34*	2.76*	0.64	0.68	0.75	0.86*
	(0.37)	(0.50)	(1.63)	(0.94)	(0.34)	(0.36)	(0.38)	(0.46)
MEF_{50} ($l.sec^{-1}$)	3.88	4.05	4.18*	4.32*	1.15	1.18	1.25	1.29
	(0.88)	(0.96)	(0.83)	(0.95)	(0.82)	(0.76)	(0.85)	(0.82)
HR ($beats.min^{-1}$)	79.60	77.20	76	74.60	92.7	89.6	86.3	88.8
	(11.23)	(9.53)	(8.43)	(7.95)	(20.4)	(17.1)	(16.4)	(12.2)

* Significantly different from control value ($P < 0.05$).

increase in lung function indices was less after the buccal route than after inhalation, there was no significant difference between the two routes after 60 minutes, except for sGaw (higher for the inhalation route), and heart rate (lower for the buccal route) (Table III and Fig. 1). In individual subjects MEFR and sGaw did not always change in the same direction. Indeed, in some subjects an increase in sGaw coincided with a decrease in MEFR.

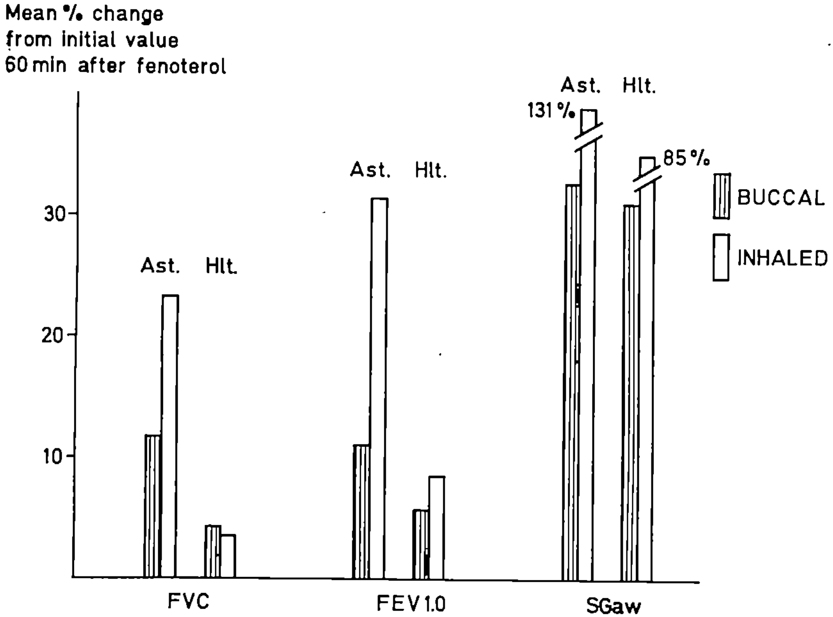

Fig. 2. Mean percentage changes in FVC, $FEV_{1.0}$ and sGaw 60 minutes after administration of fenoterol by both routes in healthy subjects (Hlt.) and asthmatic patients (Ast.)

Table III. Comparison between buccal and inhalated fenoterol (60 minutes after administration) in normal subjects and asthmatic patients, *P* values (and significance levels)

	Normal subjects	*Asthmatic patients*
FVC	0.23 (NS)	1.43 (NS)
FEV_1	1.35 (NS)	3.78 (0.01)
RV	0.41 (NS)	−1.00 (NS)
sGaw	3.28 (0.01)	2.77 (0.025)
MEF_{50}	1.11 (NS)	2.58 (0.05)
HR	4.22 (0.005)	1.05 (NS)

Asthmatic subjects

There were no significant differences between pretreatment values on the two days. Inhalation of fenoterol was followed by a rapid (five minutes) and large change of $FEV_{1.0}$, sGaw and MEFR and static lung volumes (TLC, RV) (Table I). This increase reached its maximum after 30 and 60 minutes (Fig. 2).

After buccal administration of fenoterol all static lung volumes improved and bronchial calibre as assessed by $FEV_{1.0}$ and sGaw was also significantly increased (Table II and Fig. 2). However, increase of MEFR did not reach a statistically significant level (Table II).

Buccal administration produced smaller changes than inhalation, $FEV_{1.0}$, MEFR and sGaw being significantly higher after inhalation (Table III). Heart rate decreased, but not significantly, after both routes (Fig. 1). As in normal subjects sGaw and MEFR changed in opposite directions in some patients.

Comparison between healthy subjects and asthmatic patients

After inhalation of fenoterol FVC (after five minutes) increased to 117% of pretreatment value in asthmatic patients compared to 103% in healthy subjects. Similarly, $FEV_{1.0}$ (127% in asthmatics *v.* 108% in normals), PEFR (122% in asthmatics *v.* 104% in normals) and MEF_{50} (150% in asthmatics *v.* 123% in normals) showed larger changes in the asthmatic group and these differences between groups were statistically significant. Total lung capacity and RV decreased in the asthmatic group to 95% and 78% of the respective pretreatment values, while in normal subjects they were only slightly reduced. Again, the differences between the two groups were significant. Five minutes after inhalation of fenoterol heart rate was significantly lower in the asthmatic than in the normal group. After 30 and 60 minutes of fenoterol inhalation lung function indices were still significantly different between the two groups, while heart rate was no longer so.

After buccal administration of fenoterol TLC (60 minutes) decreased in asthmatic patients to 95% of pretreatment value whereas in healthy subjects TLC increased slightly (102%). This difference was statistically significant, but other indices did not differ statistically between the two groups.

Side effects

Nine out of 10 normal subjects experienced moderate tremor or palpitations after inhalation of fenoterol. Only one healthy subject experienced tremor after buccal administration of the drug. No asthmatic patient had side effects by either of the two routes.

Discussion

Changes in lung function tests after inhalation of fenoterol, in our normal subjects as well as in asthmatic patients are similar to those previously published (Bobbaers et al. 1976; De Troyer et al. 1978). In both groups an increase in bronchial calibre was demonstrated by an improvement in sGaw, $FEV_{1.0}$ and MEFR. In the asthmatic patients inhalation of fenoterol resulted in larger increases than in healthy subjects. In a few subjects a decrease in MEFR, instead of an increase, was recorded after fenoterol inhalation. Similar results were previously reported by Bobbaers et al. (1976) and are probably related to increased collapsibility of the bronchi induced by fenoterol.

The significant bronchodilation observed in healthy subjects after both inhalation and buccal administration of fenoterol confirms previous findings (Bobbaers et al. 1976). We suggest that trials on new bronchodilator drugs may also be done on normal subjects and indeed, these offer the great advantage over asthmatic patients of a steady functional status.

After buccal administration of fenoterol, a slight but significant increase in FVC was seen after five minutes in asthmatic patients. Most indices were significantly different from control values after 30 and 60 minutes in both healthy subjects and asthmatic patients and effects were observed on both bronchial calibre and lung volumes. The buccal route therefore proved effective in inducing bronchodilation, strongly suggesting that the drug was absorbed from the oral mucosa into the blood stream. Bronchodilation was less following buccal administration than after inhalation in both normal subjects and asthmatic patients, probably due to the local effect of β_2-agonists on the bronchial receptors (Clark 1979).

Present methods do not permit plasma measurements of the minute concentrations of fenoterol reached after inhalation or buccal administration. One could therefore argue that a small proportion of buccally administered fenoterol might have been inhaled, but this is improbable after the precautions we took to avoid inhalation. Moreover only about 10% of an inhaled dose of a bronchodilator reaches the lung (i.e. about 20 μg for an inhaled dose of 200 μg). Had our subjects inhaled a small amount of buccally administered drug only 10% of which had reached the lung it is unlikely that such a small dose could produce a significant increase of several indices of lung function over control values.

Previous data support our findings. Schuman and Herxheimer (1971) found rapid bronchodilation (increases ranging between 20 and 100%) after sublingual administration of 5 and 10 mg salbutamol tablets. The onset of action after sublingual administration was 15 to 45 minutes earlier than after oral administration of a similar dose, precluding the possibility that the results were due to swallowing of the saliva after sublingual administration. Ruffin et al. (1978) compared the effect of inhaling fenoterol to holding a solution containing 500 μg of fenoterol in the mouth for two minutes and to placebo administration, in 10 asthmatic patients. The inhaled route was found to give significantly better results than either buccal route or placebo, but no comparison was made between placebo and buccal fenoterol. From their results (Figs 1 and 2 in their paper), it appears that buccal fenoterol produced a significant greater increase in $FEV_{1.0}$ than placebo. At variance with these results, Martin et al. (1979) found no significant spirographic change after fenoterol nebulization into the mouth of five asthmatic children.

Tremor of hands, palpitations and a slight increase in heart rate were observed in almost every normal subject after inhalation of fenoterol suggesting that the drug was absorbed through the bronchial mucosa into the blood stream to reach muscle and cardiac receptors (Simonsson et al. 1974). Indeed, a rise in plasma levels of fenoterol has been found after its bronchial instillation (Laros et al. 1977). The absence of side effects in asthmatic patients following inhalation of fenoterol does not necessarily imply a lack of bronchial absorption but confirms the findings of Svedmyr et al. (1974) of a decrease in side effects and tachycardia after chronic administration of β_2-agonists. All our asthmatic patients were on chronic treatment with β_2-agonists, while normal subjects were receiving fenoterol for the first time. The lesser side effects and changes in heart rate after buccal administration than after inhalation may be explained by the difference in absorption due to the different surface area of the buccal and bronchial mucosa.

We conclude that buccal administration of fenoterol induced significant bronchodilation, though less than after inhalation. Buccal administration of β_2-agonists may be useful in children and elderly patients who are unable to learn a correct inhalation technique. In these patients a less efficient inhalation could be partially compensated for by absorption through the oral mucosa. Sublingual administration of bronchodilators, which appears to be followed by a more rapid onset of action than the oral route (Schuman & Herxheimer 1971) may represent a useful alternative to inhalation and deserves further study.

Acknowledgements

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Br. J. Dis. Chest (1982) *76*, 374

THE USE OF THE 12 MINUTE WALKING TEST IN ASSESSING THE EFFECT OF ORAL STEROID THERAPY IN PATIENTS WITH CHRONIC AIRWAYS OBSTRUCTION

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Summary

The reproducibility of the 12 minute walking distance (12 MD) was assessed in ten men with chronic airways obstruction, and the 12 MD was used, together with spirometry, transfer factor and three subjective assessments of breathlessness to evaluate the effects on respiratory function of prednisone 30 mg daily given orally in double-blind placebo-controlled fashion for two weeks. Like others, we found the 12 MD reproducible on a single day with a mean variation of 3.1%. Tests performed two weeks apart showed greater variability ranging from 0.2% to 30.9%, (mean 9.1%). During placebo and prednisone therapy the 12 MD and assessments of breathlessness correlated significantly with each other and with TLCO, but not with spirometry.

Following steroid therapy there was a significant increase in mean TLCO but no significant change in 12 MD, spirometry or subjective assessments. Changes in 12 MD and TLCO correlated significantly with each other and with changes in subjective assessments. Changes in FEV_1 correlated with changes in breathlessness, and also with variability in FEV_1 while receiving placebo. Individuals with the greatest changes in 12 MD and FEV_1 were those with the greatest variability on placebo.

The variability of the 12 MD and FEV_1 should be measured in individuals before using these tests to assess response to steroid therapy.

Introduction

Respiratory disability and response to therapy in patients with chronic airways obstruction is usually assessed by spirometry. Previous trials of corticosteroid therapy in such patients have shown variable changes in spirometry (Freedman 1963; Evans et al. 1974; Sahn 1978). Some authors have reported subjective improvement despite a lack of objective increase in forced expiratory volume in one second (FEV_1) (Williams & McGavin 1980). Some attribute this subjective response to the euphorient effect of steroids, while others feel that patients may be experiencing a real improvement in function which is not detected by spirometry. Indeed many physicians now believe that measurement of changes in respiratory disability in such patients should include tests of exercise performance and a quantifiable assessment of symptoms.

The distance walked by patients at their own pace in 12 minutes (the 12 minute distance – 12 MD), is a reproducible test which is less variable than spirometry (McGavin et al. 1976; Mungall & Hainsworth 1979) and correlates with exercise maximum oxygen uptake and ventilation, forced vital capacity (FVC) and subjective assessment (McGavin et al. 1976, 1978). In a single-blind study of steroid therapy, Williams and McGavin (1980) showed that patients' assessment of the effects of treatment correlated with change in FVC, suggesting that the euphorient effect of steroids does not eclipse their specific action on ventilatory function.

We have studied ten patients with chronic airways obstruction measuring spirometry, transfer factor, 12 minute distance and subjective assessments of breathlessness in a double-blind, placebo-controlled trial in an attempt to discover whether or not they had steroid responsive airways obstruction. We were particularly interested to determine whether steroid therapy increased their 12 minute distance. We have also assessed the reproducibility and correlation between these tests.

Patients

We studied ten men aged 52 to 70 years (mean age 61 years). Eight had chronic bronchitis according to the criteria of the Medical Research Council (Stuart-Harris et al. 1965) and two had radiological features of emphysema (Laws & Heard 1962). All had chronic airways obstruction with a mean FEV_1 of 810 ml (range 600 to 1050 ml; SD ± 210 ml) and mean FVC of 2560 ml (range 1750 to 3600 ml; SD ± 593 ml) at body temperature and pressure saturated (BTPS). At the start of the trial we measured changes in spirometry after inhalation of 10 mg isoprenaline. The mean increase in FEV_1 was 160 ml (range 90 to 260 ml; SD 50 ml) and in FVC was 750 ml (range –100 to 1030 ml; SD 330 ml). None of the patients had previously received oral steroids. Throughout the study all patients received two puffs of a β-stimulant bronchodilator four times daily.

Design of the trial

In addition to their usual therapy the patients received placebo tablets initially (two tablets three times daily) for two weeks and were then randomized into two equal groups. One group then received active prednisone (two 5 mg tablets thrice daily) for two weeks followed by placebo (two tablets thrice daily) for a further two week period. The patients in the second group received these tablets in reverse order. Objective measurements and subjective assessments were made at the start of the trial and after each treatment period in double-blind fashion. When analysing the results we compared values obtained after two weeks of prednisone therapy with those measured at the end of the previous placebo fortnight in order to avoid any therapeutic carry-over from the active prednisone.

Objective measurements

FEV_1 and FVC were measured using a Vitalograph dry spirometer and expressed as the best of three readings at BTPS. Exercise tolerance was measured by a self-paced 12 minute walk, as described by McGavin et al. (1976). Patients were asked to walk as far as possible during a 12 minute period, but permitted to stop and start at will. After an initial practice walk two further walks were performed with a rest of 20 minutes between them, and the mean 12 MD was used in analysis. The carbon monoxide transfer factor was measured in duplicate using the single breath method (Cotes 1975).

Subjective assessments

We made three assessments of subjective exercise tolerance. Patients recorded their subjective walking ability (SWA) daily using a questionnaire comprising a list of five grades of breathlessness adapted from those of Fletcher et al. (1959) and ranging from ability to walk just across the room (score 0) to ability to keep up with others of the same age and sex in all respects (score 5). The total score was summed for each two week treatment period. The oxygen cost diagram (OCD), previously used by McGavin et al. (1978), consists of a 100 mm line flanked by everyday activities positioned proportionally to their oxygen cost. This was shown to patients when they arrived for their laboratory tests and they were asked to mark the line at a point above which their breathlessness would not allow them to go. The result was expressed in mm above zero. After each 12 minute walk a rating of perceived exertion (RPE) was obtained using the scale devised by Borg (1970). Patients were asked to indicate the number on the scale which best represented the effort required to perform each walk, and the mean value for the two walks was used in analysis.

Statistical analysis

We used the Wilcoxon signed rank test to compare results from the prednisone fortnight with those from the placebo fortnight and calculated linear correlation coefficients by the method of least squares.

Results

Reproducibility of the 12 minute distance

We assessed the variability of the 12 MD on a single day as the percentage variation from the mean of the two walks. The mean variation was 3.1% (range 0 to 20%); of 39 pairs of walks completed, only one showed a variation of more than 8%.

We expressed the variability of the 12 MD and FEV_1 at intervals of two weeks while receiving placebo as the maximum percentage variation from the mean. Results from two tests were used in patients 3, 6, 8, 9 and 10 and from three tests in the remaining five men. For the group the mean variability in 12 MD was 9.1% (range 0.2% to 30.9%). Seven patients had variability less than 7%. The mean variability for FEV_1 was 12.1% (range 0 to 33.3%).

Effect of prednisone on objective tests

There were no statistically significant increases in 12 MD or spirometry after two weeks of placebo or after two weeks of steroid therapy (Tables I and II). The mean increase in 12 MD after prednisone was 4.6% (range −11.8% to 43.7%).

Three men (patients 2, 6 and 10) showed increases in 12 MD greater than 10%. Patient 2 with an increase in 12 MD of 10.5% showed an increase in FEV_1 of 27.3% and patient 10 with a 12 MD increase of 43.7% had an increase in FEV_1 of 14.6%.

Table I. Objective and subjective assessments before and after placebo and prednisone therapy

Patient		*12MD* (m)	*FEV*$_1$ (ml)	*FVC* (ml)	*SWA**	*OCD** (mm)	*RPE**	*TLCO* (mmol/kPa/min)
1	Baseline	637	680 (800)	2220 (2520)	–	63	12.5	2.6
	Placebo	518	660	2340	19	28	15	2.6
	Placebo	383	560	2160	13	28	15	2.6
	Prednisone	338	600	2200	11	30	13	2.5
2	Baseline	704	600 (750)	2800 (3300)	–	39	12	3.46
	Placebo	837	1000	3050	35	44	12	3.4
	Placebo	889	1100	3550	29	25	13	3.95
	Prednisone	982	1400	3950	32	73	12	4.22
3	Baseline	1058	880 (1100)	2120 (2620)	–	46	11	3.15
	Placebo	1204	650	1650	52	75	13	3.31
	Prednisone	1087	650	1850	52	54	11	4.0
	Placebo	928	850	2150	44	32	14	3.5
4	Baseline	840	1150 (1300)	2250 (2820)	–	55	14.5	4.24
	Placebo	825	1020	2220	38	30	13	3.9
	Placebo	880	980	2260	18	38	13	3.77
	Prednisone	856	980	2020	16	35	14.5	–
5	Baseline	924	1025 (1115)	3600 (3500)	–	75	13.5	4.2
	Placebo	922	1050	3350	14	30	15	4.6
	Placebo	926	1100	3950	33	43	14	4.6
	Prednisone	948	1050	3400	37	55	13	5.1
6	Baseline	898	600 (750)	2150 (2400)	–	60	11	4.18
	Placebo	883	600	1900	42	60	13	4.2
	Prednisone	980	580	2350	51	75	12	4.72
	Placebo	903	550	2200	43	43	15	4.1
7	Baseline	787	660 (810)	2420 (2570)	–	55	13	3.66
	Placebo	853	590	2280	42	53	14.5	3.4
	Placebo	853	800	3080	33	56	15.5	3.2
	Prednisone	838	700	2820	31	28	15	–
8	Baseline	999	1050 (1300)	3020 (3150)	–	75	9	6.1
	Placebo	930	900	2350	42	55	11	6.0
	Prednisone	990	950	2750	42	75	9	6.0
	Placebo	1148	960	2400	39	50	11	–
9	Baseline	655	860 (1050)	3300 (3460)	–	55	17	2.2
	Placebo	676	1000	3460	28	48	16	2.2
	Prednisone	689	1180	4060	28	50	18	2.5
	Placebo	656	940	3860	27	48	14.5	2.5
10	Baseline	364	600 (750)	1750 (2500)	–	30	14.5	2.7
	Placebo	689	820	2920	14	53	13	2.56
	Prednisone	990	940	2970	43	75	11	3.95
	Placebo	754	1150	3300	46	60	12	3.15

Figures in parentheses show results of spirometry after inhalation of 10 mg isoprenaline.

*SWA, subjective walking ability; OCD, oxygen cost diagram; RPE, rating of perceived exertion.

During placebo treatment the variability in their 12 MD had been 13.1% (patient 2) and 30.9% (patient 10) and their FEV_1 variability had been 33.3% and 15.5% respectively. Patient 6 was the third man with an increase in 12 MD after prednisone greater than 10% (10.9%). His FEV_1 fell by 3.3% and he showed negligible variability in 12 MD or FEV_1 on placebo.

One other man (patient 1) showed variability of 12 MD on placebo greater than 7% (25.5%) and he had the greatest reduction (11.7%) in 12 MD after prednisone. Patient 7 was the only other man to have FEV_1 variability on placebo greater than 15% (17.1%) and he showed the greatest fall in FEV_1 after prednisone of 12.5%.

Five patients (2, 3, 6, 8 and 9) showed increases in FVC of more than 10% after prednisone. Three (3, 8 and 9) had no comparable changes in 12 MD. Patient 9 showed an increase in FEV_1 of 18.0% with little change in 12 MD.

The only objective test to show statistically significant improvement ($P < 0.05$) following steroid therapy was the transfer factor (Table II) though in all patients the increases were very small (Table I).

Table II. Mean per cent changes in assessments after placebo and prednisone and significance

	Before placebo	*After placebo*	*Per cent change*	*P*	*After prednisone*	*Per cent change*	*P*
12 MD (m)	792.9	831.3	4.84	> 0.1	869.8	4.63	> 0.1
FEV_1 (ml)	831	851	2.41	> 0.1	903	6.11	> 0.1
FVC (ml)	2604	2678	2.84	> 0.1	2837	5.94	> 0.1
TLCO (mmol/kPa/min)	3.26	3.35	2.76	> 0.05	3.86	15.2	< 0.05
SWA*	–	30.4	–		34.3	12.83	> 0.1
OCD (mm)*	45.1	50.1	11.08	> 0.1	55.0	9.78	> 0.1
RPE*	13.0	13.65	5.0	> 0.1	12.85	–5.86	> 0.1

*See footnote to Table I.

Acute isoprenaline response and the objective effect of prednisone

Eight of the patients showed increases in FEV_1 of 15% or more after isoprenaline. The absolute increases were usually small and the mean increase for the ten patients in the study was 160 ml (SD ± 50 ml).

The changes in FEV_1 or FVC after isoprenaline did not correlate with changes after prednisone (for FEV_1, $r = 0.149$, $P > 0.1$; for FVC, $r = -0.168$, $P > 0.1$) or with changes in 12 MD after prednisone (for FEV_1, $r = 0.121$, $P > 0.1$; for FVC, $r = 0.138$, $P > 0.1$).

Effect of prednisone on subjective tests

There were no significant changes in mean values of SWA, OCD or RPE after placebo or after prednisone therapy (Table II).

Correlation between different methods of assessment

During placebo and prednisone therapy 12 MD did not correlate with either FEV_1 or FVC but was significantly correlated with TLCO. Both 12 MD and TLCO were significantly correlated with SWA, OCD and RPE (Table III).

The changes in 12 MD after steroid therapy were significantly correlated with changes in TLCO and changes in SWA and OCD (Table IV). Changes in FEV_1 after prednisone correlated with changes in OCD (Table IV), and also with variability in FEV_1 on placebo ($r = 0.664; P < 0.05$).

Changes in FVC did not correlate with any other assessments. Changes in TLCO following steroid therapy correlated significantly with changes in SWA.

Table III. Correlation of 12 MD and TLCO with spirometry and assessments of breathlessness

	FEV_1	*FVC*	*SWA*†	*OCD*†	*RPE*†	*12 MD*
12 MD	0.282	0.001	0.698***	0.496***	−0.444**	
TLCO	0.266	0.075	0.444*	0.402**	−0.590***	0.639***

†See footnote to Table I.
*$P < 0.05$. **$P < 0.01$. ***$P < 0.001$.

Table IV. Correlation between changes in different assessments after steroid therapy

	Changes of					
	12 MD	*FEV_1*	*FVC*	*SWA*†	*OCD*†	*RPE*†
12 MD		0.385	0.151	0.898***	0.639*	−0.166
FEV_1			0.615*	0.207	0.717**	0.269
FVC				0.037	0.356	0.092
TLCO	0.678*	0.104	0.127	0.884**	0.047	−0.275

†See footnote to Table I.
*$P < 0.05$. **$P < 0.01$. ***$P < 0.001$.

Discussion

We have confirmed the results of McGavin et al. (1978) that the 12 MD is reproducible on a single day. At intervals of two weeks we found greater variability, similar to that observed by Mungall and Hainsworth (1979). Three of our patients had greater than 10% variability in 12 MD while receiving placebo and greater than 15% variability in FEV_1. While such variation might reflect real changes in function especially in patients with asthma, it complicates the analysis of changes after therapeutic intervention. Mungall and Hainsworth (1979) emphasized the need to know the variability, or 'noise' of any test in any patient before results from that test are used to determine a therapeutic response. Our study confirms the importance of this for the 12 MD and FEV_1 in that two of the patients who showed marked variability in both tests on placebo were among those with the largest increases in 12 MD and FEV_1 after prednisone. Although these findings suggest that these patients may have had asthma, the third patient with marked variability in 12 MD on placebo had the greatest fall in 12 MD after prednisone, and the third patient with great variability in FEV_1 on placebo had the greatest fall in FEV_1 after prednisone. Thus although the diagnoses of chronic bronchitis, emphysema and asthma are obviously not mutually exclusive, improvement in objective tests following steroid therapy in patients with marked variability may simply reflect that variability, and cannot necessarily be construed as a positive response to therapy.

There were no overall changes in spirometry or in subjective assessments when results after two weeks of prednisone were compared with those after the previous two weeks of placebo. Because of this and the variability in the assessment discussed above, no firm conclusions can be drawn from the results of individual patients. Apart from the two patients in whom the variability of the 12 MD and FEV_1 was so large, only one patient increased his 12 MD by more than 10% after prednisone. Although this was accompanied by a large rise in FVC and improvement in all three subjective assessments, his FEV_1 fell by 3.3%. Two other patients showed an improvement in FVC of more than 10% after prednisone with no comparable change in 12 MD or FEV_1 and one patient showed increases in all three subjective assessments with no change in 12 MD or spirometry.

Like Mungall and Hainsworth (1979) we found no correlation between 12 MD and either FEV_1 or FVC. McGavin et al. (1976) also found no correlation between 12 MD and FEV_1 but in their study 12 MD did correlate with FVC and subsequently (McGavin et al. 1978) they found that 12 MD correlated with both FEV_1 and FVC. Spirometry is a simple test of mechanical lung function and as such reflects only one of a number of factors determining exercise tolerance. McGavin et al. (1976) found that 12 MD correlated with oxygen consumption measured during exercise on a cycle ergometer. The oxygen cost diagram (McGavin et al. 1978) was designed to reflect the oxygen consumption associated with everyday activities (Durnin & Passmore 1967) and like McGavin et al. (1978) we observed a strong correlation between 12 MD and OCD. In view of these findings it is understandable that the 12 MD increases after physical training programmes designed to improve cardiovascular and muscle fitness, while spirometry usually remains unaltered (Holten 1972; McGavin et al. 1977; Mungall & Hainsworth 1980; Sinclair & Ingram 1980). It would perhaps be surprising if the same pattern were observed following steroid therapy direct at the airways, though further studies are required to determine whether or not this ever occurs.

The only objective resting test with which 12 MD correlated was the carbon monoxide transfer factor as in the study of Mungall and Hainsworth (1979). The significant correlation of both 12 MD and TLCO with the three subjective assessments and the correlation of changes in each with SWA indicates that patients' own assessments of their ability reflects objective function. Subjective walking ability recorded daily and summed for each two week period and results from the oxygen cost diagram showed the highest correlations with 12 MD and changes in SWA were also highly correlated with changes in 12 MD. We think it is likely that one of the subjective assessments may prove helpful in assessing changes in fitness in patients with chronic airways obstruction, and may obviate the need for the time consuming measurement of 12 MD.

Changes in spirometry after isoprenaline in these patients could not be used to predict steroid responsiveness. The dose–response characteristics of airways obstruction to oral steroid therapy in this group of patients have not been adequately defined. Most studies which have attempted to assess steroid responsiveness in such patients have used daily doses of at least 30 mg prednisolone (Webb et al. 1981). Such studies should continue for at least 11 days (Webb et al. 1981). Incorporation into the trial of a preceding fortnight when the patient receives identical placebo tablets provides valuable information about placebo response and variability of objective tests. Our study confirms the importance of assessing the latter when interpreting individual responses to steroid therapy.

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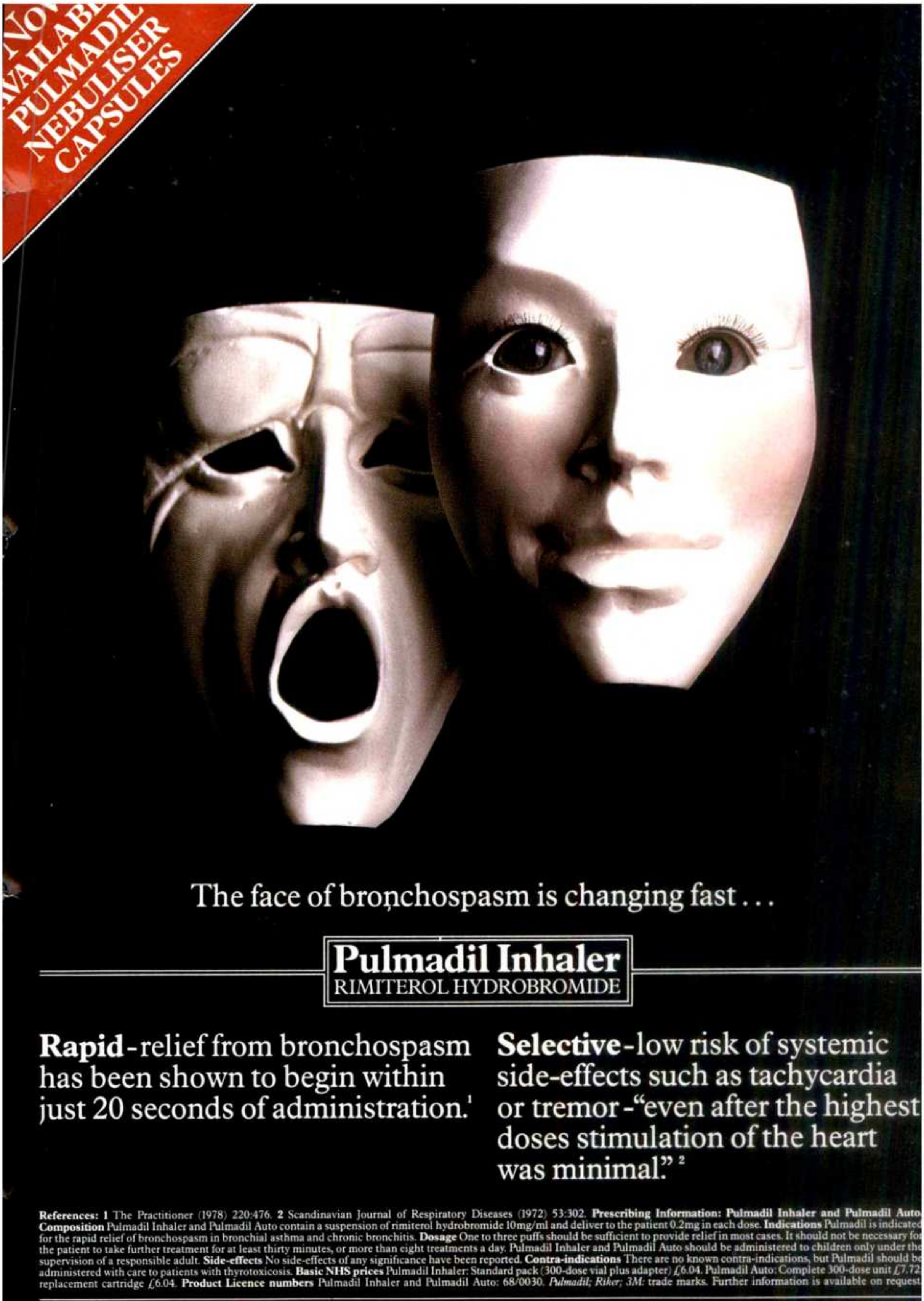

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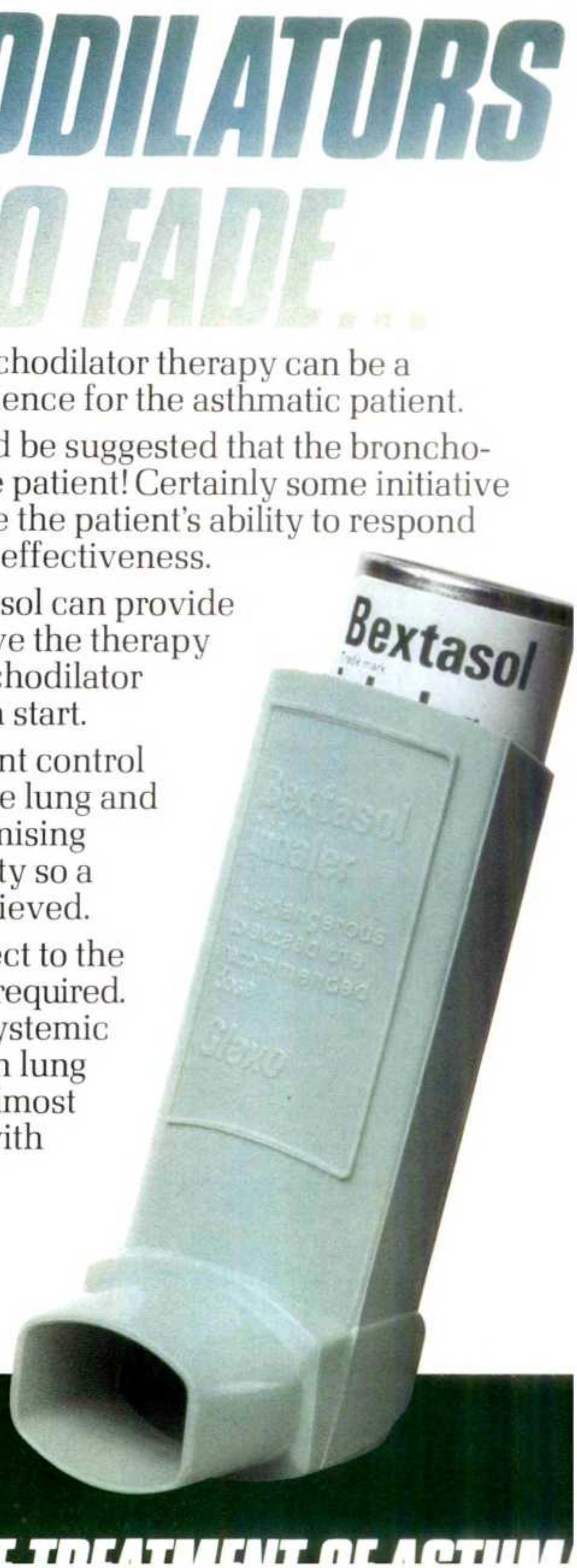

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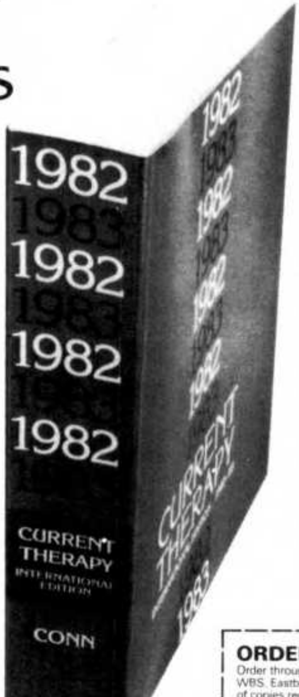

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A DOUBLE-BLIND CLINICAL TRIAL OF KETOTIFEN AND DISODIUM CROMOGLYCATE IN BRONCHIAL ASTHMA

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Summary

A double-blind cross-over trial compared the efficacy of ketotifen (1 mg b.d.) and DSCG (20 mg q.d.s.) as prophylactic therapy for asthma. It involved two eight-week periods of active therapy, each being preceded by two weeks of double placebo treatment. Analysis of symptoms recorded on diary cards showed that there was a reduction in the cough score in the atopic asthmatics on DSCG compared to ketotifen, and reductions in the cough score, wheeze and dyspnoea on DSCG when compared with placebo. There was a significant reduction in the diurnal variation in PEFR during treatment with DSCG compared to ketotifen and improvement in morning PEFR on DSCG compared with placebo. It was concluded that DSCG resulted in a significant therapeutic effect during the trial, whereas ketotifen (1 mg b.d.) did not.

Introduction

Since the introduction of disodium cromoglycate (DSCG) for the prophylaxis of bronchial asthma, a number of orally active antiallergic drugs have been investigated. Only one of these, ketotifen (Zaditen-Sandoz), has been found suitable for clinical use. It possesses antihistamine and mast cell stabilizing properties (Craps et al. 1978; Mattson et al. 1979) and appears to be as effective in most studies as DSCG in inhibiting the bronchial response to inhaled allergens (Pauwels et al. 1978). The results of clinical trials of ketotifen for the longer term management of asthma have varied from a therapeutic effect comparable with DSCG to no advantage over placebo (Mattson et al. 1980; Stangl et al. 1980; Szczeklik et al. 1980). This paper reports the results of a clinical trial comparing ketotifen with DSCG in the maintenance treatment of patients with asthma.

Methods

A double-blind cross-over design lasting 20 weeks was chosen. It involved two eight-week periods of treatment with ketotifen 1 mg twice daily or DSCG 20 mg four times a day in random order, each being preceded by a two week period of placebo treatment (Fig. 1). Tablets and spincapsules containing either placebo or active drug were taken throughout the trial. Active and placebo treatments were identical in appearance.

Patients with bronchial asthma, aged between 16 and 70 years, regularly attending asthma clinics gave informed consent to the trial. All had documented reversibility of airways obstruction and variability of forced expiratory volume in one second (FEV_1) of at least 20% prior to entering the trial. Those with an FEV_1 of less than 30% of the predicted value, smokers, those with any concomitant illness, pregnancy, or with poor inhaler technique were excluded. The clinical and physiological characteristics of the patient population are shown in Table I.

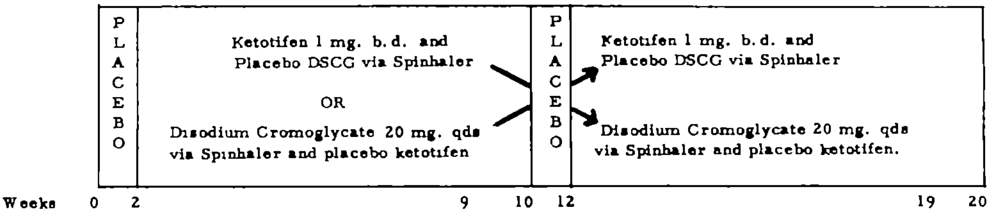
P L A C E B O
Ketotifen 1 mg. b.d. and
Placebo DSCG via Spinhaler
OR
Disodium Cromoglycate 20 mg. qds
via Spinhaler and placebo ketotifen
P L A C E B O
Ketotifen 1 mg. b.d. and
Placebo DSCG via Spinhaler
Disodium Cromoglycate 20 mg. qds
via Spinhaler and placebo ketotifen.
Weeks
0
2
9
10
12
19
20

Fig. 1. Trial design. Tablets and spinhaler were taken throughout, one or both containing placebo according to the stage of the trial. Comparisons were made between the two drugs during weeks 9 and 10 and 19 and 20, and between each drug and placebo during weeks 1 and 2 and 9 and 10, and weeks 11 and 12 and 19 and 20

Table I. Clinical characteristics of the patients

Number entering trial	32
Male/female	15/17
Mean age (years)	44 (range 20–70)
Type of asthma	
Atopic	23
Non-atopic	9
Pretrial therapy	
Oral corticosteroids	9
Inhaled corticosteroids	22
DSCG	11
Bronchodilators only	3

On starting the trial DSCG, where taken, was stopped and the trial drugs instituted. Thereafter, depending upon symptoms and the clinical state of the patients, patients were advised to reduce concomitant therapy if possible. In the event of exacerbations, a standardized treatment protocol was used, consisting of a short course of oral corticosteroids in reducing doses for eight days and antibiotics where necessary.

Throughout the trial patients completed a diary card twice daily, recording the severity of their asthmatic symptoms, using a simple point scoring system, which included frequency and severity of cough, breathlessness on exertion, the number of attacks of wheezing occurring during the day, and the number and severity of nocturnal attacks of wheeze and cough. Patients also recorded the best of three peak flow rate measurements (PEFR) using a Wright's mini peak flow gauge (Clement Clarke International Ltd) at the same time in the morning and evening prior to bronchodilator therapy, and also the treatment taken, in addition to the trial drugs, for the routine management of their asthma.

Patients attended the clinic at the end of weeks 2, 6, 10, 12, 16 and 20, when spirometry was performed, diary cards were collected, blood was taken for routine haematological and biochemical investigations, and patients were advised to reduce concomitant therapy where appropriate.

Statistical analysis

Mean values were calculated for diary card scores, concomitant treatment dosages, and morning and evening PEFR results for each week of the trial. As there was no significant difference in any of these indices during either of the two placebo periods it was possible to compare periods of one half of the cross-over study with equivalent periods of the other. Thus, a comparison of weeks 9–10 and 19–20 represent a direct comparison of the effects of ketotifen and DSCG during those periods. Moreover, as the two placebo periods did not differ, and as they preceded the periods of active treatment, it was possible to compare the last two weeks of treatment with either drug directly with the placebo treatment, to determine the presence of a therapeutic effect over the course of treatment with that drug.

Wilcoxon's signed rank sum test was used throughout for the assessment of non-parametric symptom score indices. Student's *t*-test was used for analysis of spirometry and PEFR results.

Although 32 patients entered the trial only the results of the 28 patients who completed it have been analysed.

Results

Symptom scores

The cough score was significantly better in the atopic asthmatics during treatment with DSCG ($P < 0.05$). No other significant differences emerged on direct comparison of the two drugs (Table II).

The symptom scores during the last two weeks of active treatment with either drug were also compared with those obtained during the preceding placebo period (Table III). DSCG therapy led to a significant improvement in the scores for the

Table II. Results of comparison of ketotifen and DSCG — Wilcoxon's signed rank sum test

Symptom score	*All patients* (n = 28)			*Atopic asthmatics* (n = 19)		
	Rank sum		*P*	*Rank sum*		*P*
	Ketotifen	DSCG		Ketotifen	DSCG	
Cough	111	42	NS	75	16	$P < 0.05$
Daytime attacks of wheeze	68	52	NS	37.5	28.5	NS
Nocturnal symptoms of asthma	74.5	78.5	NS	50.5	54.5	NS
Severity of dyspnoea	71.5	19.5	$P < 0.1$	50	16	NS

symptoms of cough ($P < 0.02$), wheeze ($P < 0.05$), and dyspnoea ($P < 0.05$). A similar improvement did not occur with ketotifen.

Spirometry

There was no significant difference between ketotifen and DSCG for either morning or evening PEFR, but there was a highly significant reduction in the difference between the evening and morning PEFR (diurnal variation) during the last two weeks of treatment with DSCG compared with the equivalent period of treatment with ketotifen (Table IV).

There was a significant improvement in the morning PEFR during the last two weeks of active therapy with DSCG compared with the preceding placebo period, but no improvement in either morning or evening PEFR could be demonstrated during the last two weeks of ketotifen therapy compared with the preceding placebo period.

There was no difference in the FEV_1 performed at the clinic visits, during any period of the trial.

Table III. Results of comparison of placebo (rank 1) with ketotifen or DSCG (rank 2) – Wilcoxon's signed rank test

		All patients ($n = 28$)			*Atopic asthmatic* ($n = 19$)		
Symptom score	*Comparison of placebo with*	*Rank sum* 1	2	*P*	*Rank sum* 1	2	*P*
Cough	Ketotifen	99.5	110.5	NS	34.5	85.5	NS
	DSCG	115	21	$P < 0.02$	69.5	8.5	$P < 0.02$
Daytime attacks of wheeze	Ketotifen	96.5	93.5	NS	33.5	57.5	NS
	DSCG	166	44	$P < 0.05$	106.5	29.5	$P < 0.1$
Nocturnal symptoms of asthma	Ketotifen	76	44	NS	30.5	24.5	NS
	DSCG	103	50	NS	70.5	20.5	$P < 0.1$
Severity of dyspnoea	Ketotifen	40.5	37.5	NS	16	20	NS
	DSCG	99	21	$P < 0.05$	54	12	$P < 0.1$

Table IV. Mean PEFRs (litres/minute) during the last two weeks of active therapy with each drug and the preceding placebo period. (Student's *t*-test for paired differences)

	Ketotifen ($n = 28$)		*DSCG* ($n = 28$)	
	Active period	*Previous placebo period*	*Active period*	*Previous placebo period*
Evening PEFR	363 ± 18.7	347 ± 18.5	353 ± 18.8	353 ± 18.8
Morning PEFR	312 ± 16.7	315 ± 17.8	329 ± 18.1(3)	310 ± 17.9(3)
Diurnal variation	50 ± 10.1(1)	32 ± 11.9	25 ± 7.8(1)(2)	43 ± 10.6(2)

(1) Diurnal variation, DSCG *v.* ketotifen, $P = 0.001$; (2) Diurnal variation, DSCG *v.* placebo, $P = 0.03$; (3) Morning PEFR, DSCG *v.* placebo, $P = 0.01$.

Concomitant therapy

There was no reduction in bronchodilator consumption at any period during the trial. Two out of the nine patients who were maintained on oral corticosteroids prior to entering the trial did manage to reduce their daily dose of corticosteroid, one while receiving ketotifen, the other while receiving DSCG.

Treatment failures

Four patients were withdrawn from the trial due to persistent severe asthma, two while taking DSCG and two on ketotifen. The two who relapsed during ketotifen therapy had been well maintained on DSCG before the trial. One of the patients relapsing during DSCG treatment had previously tried it unsuccessfully. The other relapse on DSCG had never tried the drug, but had completed the first active treatment period of the trial on ketotifen.

Side effects of therapy

No major side effects were noted. Two patients complained of drowsiness with ketotifen, resolving by the end of the first week, and two complained of transient abdominal discomfort during the third and fourth week of ketotifen therapy. No changes in biochemical or haematological indices, measured throughout the trial, were noted.

Discussion

Two differences emerged between the two active drugs in that there was a reduction in the cough index in the atopic asthmatics, and a highly significant reduction in the diurnal variation in PEFR during treatment with DSCG compared with ketotifen. Although the trial was designed to compare the efficacy of ketotifen and DSCG as prophylactic therapy for asthma, comparison of each drug with the preceding placebo period represents the therapeutic effect of that drug. Significant improvements in symptom scores and morning PEFRs were found between periods of DSCG and placebo which could not be demonstrated during equivalent periods of treatment with ketotifen.

Other clinical trials of ketotifen have also produced disappointing results, although minor improvements in symptoms or spirometry during treatment have been reported. The British Thoracic Association (BTA) (Dyson & Mackay 1980) showed that the higher of the two recommended doses, ketotifen 2 mg twice daily, resulted in a minor but statistically significant improvement in symptoms compared with placebo, but only in patients not already receiving inhaled corticosteroids. In the same trial it was found that ketotifen 1 mg twice daily conferred no advantage over placebo. Several of the studies of parallel design comparing ketotifen 1 mg twice daily and DSCG have demonstrated significant improvement in spirometry and reduction in symptoms which was similar during both treatments (Stangl et al. 1980; Szczeklik et al. 1980). However, the most comprehensive trial of this design, which included a placebo treated parallel control group, showed that neither ketotifen nor DSCG resulted in a significant therapeutic effect (Mattson et al. 1980).

With one exception (Grant et al. 1967) other papers on DSCG have reported considerable subjective benefit in adult asthmatics (Brompton Hospital/MRC Collaborative Trial 1972; Northern General Hospital, Brompton Hospital & MRC Collaborative Trial 1976), but the improvement is not always reflected by increases in the FEV_1 in all the patients (Howell & Altounyan 1967; Moran et al. 1968; Robertson et al. 1969). We were unable to show any improvement in spirometry performed at the clinic visits, although DSCG produced a reduction in the diurnal variation (morning dipping) in PEFR when compared to ketotifen and placebo. Ketotifen did not produce any improvement in airways function.

Despite being unable to demonstrate the steroid sparing effect previously reported with ketotifen (Lane 1980) and DSCG (Arner et al. 1971) our findings are in keeping with the results of previously published clinical trails of both agents. DSCG does appear to confer some benefit to adult asthmatics such as those who participated in this trial; ketotifen, 1 mg twice daily, does not.

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Re: Murphy, D. & Lane, D. J. (1981) *Br. J. Dis. Chest 75,* 91.

Pleural effusion in allergic bronchopulmonary aspergillosis: two case reports

One of the two patients described in the above report as having pleural effusion due to bronchopulmonary aspergillosis has subsequently died. The post mortem demonstrated diffuse lymphoma. As the report listed above stated, a lymphocytic pleural effusion was first noted in October 1978, it responded to steroid therapy, but continued to recur at intervals throughout the next three years. The only other features were of airways obstruction and serological evidence of bronchopulmonary aspergillosis. A left supraclavicular node developed in October 1981 when he entered a gradual decline, dying on 11 April 1982. Autopsy report showed evidence of widespread lymphoma and there is no escaping the conclusion that despite the long history the original effusion was probably due to the lymphoma rather than being directly associated with the bronchopulmonary aspergillosis.

Desmond Murphy
Donald J. Lane

Br. J. Dis. Chest (1982) *76*, 390

EXPOSURE TO CARBON MONOXIDE IN SMOKERS OF MIDDLE- AND LOW-TAR CIGARETTES

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Summary

The carbon monoxide (CO) exposure of habitual middle-tar (MT) and low-tar (LT) smokers was studied in a group of 78 subjects (38 male and 40 female). CO intake from a single cigarette (measured by the rise in expired-air CO concentration) was significantly less in LT smokers. Longer term exposure, measured by pre-smoking CO levels, was also less in LT smokers, but not significantly so. A CO-based index showed that LT cigarettes were relatively more intensively smoked.

Exposure to nicotine and tar was estimated by applying the index of smoking intensity to the standard nicotine and tar yields of the brands smoked. Although an indirect estimate, the results suggest that the intake of tar and nicotine is likely to be appreciably less in LT smokers than in their MT counterparts. The likely difference in intake, however, is not as great as the difference in smoking-machine yields.

Introduction

The 1977 report of the Royal College of Physicians asserted (p. 121) that 'if, as might be possible, the harmfulness of cigarettes were reduced at least by one half, as much illness would be prevented as by the formidable task of persuading every other smoker to stop'. Not surprisingly, the question of whether smoking existing low-tar (LT) cigarettes is likely to be less hazardous than smoking middle-tar (MT) brands has been the subject of debate in both the medical and lay press (Jarvis & Russell 1980; Raw & Jarvis 1980; Stepney 1980). There is a clear dose–response relationship between disease caused by smoking and exposure to smoke constituents (Surgeon General 1981). In advance of clear epidemiological data the assertion that a particular kind of cigarette is likely to be less hazardous therefore rests on the demonstration that smokers of that kind of cigarette are less exposed than their peers to toxic smoke constituents.

Experiments in which MT smokers have been *switched* to LT cigarettes have shown that intake of CO and nicotine is reduced, although the reduction in exposure is far less than would be expected on the basis of machine-smoked yields (Turner et al. 1974; Ashton et al. 1979). However, three factors detract from the relevance of such evidence to the campaign designed to persuade smokers to adopt less hazardous smoking habits. First, smokers changing on the 'open market' from a higher to a LT brand are not, as with many of the subjects of experiment, ignorant of the brand change, or ill-disposed towards it. Secondly, smokers changing deliberately to LT cigarettes would be expected to persevere with the brand, and their smoking behaviour might undergo a relatively long period of adaptation. Thirdly, a proportion of current LT smokers will have started to smoke using LT brands, and will therefore never have experienced the marked reduction in delivery that occurs in brand-switching studies. A fair assessment of the health benefits likely to flow from the current emphasis on LT brands therefore requires either of two rather different approaches. The first is to look at the effect of brand-switching in a group of MT smokers who have expressed the *wish* to switch permanently to LT brands, and to follow this group over a long period. The second approach, and that followed here, is to compare *habitual* LT smokers with *habitual* MT smokers.

This approach has been used before, in studies of a group of extremely heavy and predominantly female smokers attending an anti-smoking clinic (Russell et al. 1980) and of a large group of middle-aged male smokers involved in a private health screening programme (Wald et al. 1980). In addition, a small-scale study considered CO and nicotine intake in groups of MT and LT smokers of unspecified status (Rawbone et al. 1978). The evidence from these studies is conflicting. As far as is known, no previous study has attempted to assess the relative smoke exposure of a large group of habitual MT and LT smokers representative in sex distribution and cigarette consumption of the wider smoking population.

For three reasons, the present study concentrates on CO exposure. First, intake of CO may be reliably and non-invasively measured (Jarvis et al. 1980) and in a way which minimizes disruption of natural smoking behaviour. Secondly, as Ashton et al. (1981) have shown, pre-smoking CO levels correlate highly with long term exposure to nicotine, and a CO-based index of smoking intensity reliably predicts the relative exposure to nicotine of populations smoking different kinds of cigarette. CO measures have also been used by Wald et al. (1980) to estimate relative exposure to tar. Thirdly, there is increasing concern that the deeper inhalation of smoke may result in LT smokers being *more* exposed to CO than MT smokers, and therefore at greater risk from cardiovascular disease (Greenhalgh 1981; Surgeon General 1981). The assessment of exposure to CO is therefore of considerable interest in its own right.

Subjects and Methods

Subjects

Seventy-eight volunteers (40 MT smokers, 38 LT) were included in the analysis. All had been smoking their usual brand of cigarettes for at least six months; all said they inhaled and were in good health. The characteristics of the LT and MT smokers (Table I) show the groups to be well matched for age, sex, cigarette consumption and time of laboratory attendance. The average number of cigarettes smoked by the group was virtually identical to the national average self-reported consumption of 19 per day (Lee 1976). Subjects were recruited for long term brand-switching experiments, but in this paper only data on their own brands will be considered.

Cigarettes

The delivery characteristics of subjects' own brands, as determined by standardized machine-smoking according to procedures used by the Laboratory of the Government Chemist, are shown in Table II. All cigarettes were commonly available UK-manufactured, filter-tipped, king size brands composed predominantly of flue-cured tobacco.

Measures

After an initial attendance to familiarize themselves with the equipment, subjects came to the laboratory on either two or three occasions and smoked a single cigarette through a small holder. Directly before and after smoking, a sample of exhaled air was obtained. Subjects inhaled, held their breath for 20 seconds and then exhaled into two collection bags. The first 500 ml of exhalate was discarded, and the CO concentration of the remaining sample measured using a Series 2000 Ecolyzer (Energetics Science Inc., Elmsford, New York). The machine used, calibration procedure and method of sample collection are as described by Jarvis et al. (1980), except that in the present study post-smoking samples were obtained within 2 minutes of extinguishing the cigarette rather than after 4 minutes. Jarvis et al. report a correlation between expired-air CO and carboxyhaemoglobin levels of $r = 0.98$ in a sample of 182 normal smokers. The accuracy of expired-air CO as an indirect measure of COHb levels has been confirmed by Wald et al. (1981) who found a correlation of $r = 0.97$ between the two measures. The manufacturers of the Ecolyzer claim an accuracy of 1 p.p.m. CO over the range of concentration found in smoking studies, and this claim has not been disputed.

Table I. Mean (± SD) age and cigarette consumption, and time of laboratory attendance, of MT and LT smokers

Tar group	*n*		*Age* (years)	*Own brand consumption* (cigs/day)	*Laboratory attendance* a.m.	p.m.	*Number of cigs smoked preattendance*	*Time since last cig* (min)
Middle	40	20 M 20 F	33 ± 10	18 ± 7	13	27	6.8 ± 4.2	68.7 ± 40
Low	38	18 M 20 F	32 ± 10	19 ± 11	10	28	7.3 ± 5.5	67.6 ± 35

Table II. Mean (± SD) standard deliveries of cigarettes smoked (mg)

Tar group	*Nicotine*	*Tar*	*Carbon monoxide*
Middle	1.52 ± 0.12	18.4 ± 0.8	18.2 ± 1.3
Low	0.86 ± 0.12	9.4 ± 0.6	11.7 ± 1.3
$\frac{\text{Low}}{\text{Middle}}$ %	57	51	64

The rise in CO concentration over the period of smoking provided a measure of the relative intake of CO from a single cigarette, whilst the pre-smoking CO level reflected intake of CO from a longer term period of smoking outside the laboratory. Pre-smoking CO levels and the rise in CO over smoking were measured at least twice in all subjects, each subject's mean value being used in the subsequent analysis. In each case subjects smoked their usual brand of cigarette and attended the laboratory at the same time of day at intervals of one week.

To establish whether CO concentrations were similar when the same subjects smoked the same brand of cigarette on different occasions, values obtained on subjects' first attendance were compared with those obtained on the second. The two measures of pre-smoking CO (unadjusted for number of cigarettes smoked and time since last smoking) correlated ($r = 0.81$), as did the two measures of CO rise ($r = 0.73$). This degree of within-subject consistency is comparable with that reported in a study involving COHb determinations (Russell et al. 1973).

Results

CO exposure

The mean pre-smoking expired-air CO concentration was slightly lower in LT smokers (Table III). However, the difference between LT and MT groups was not statistically significant, and was considerably less than the difference in machine CO yields. Standardization of pre-smoking levels (to take account of the small difference between the groups in the number of cigarettes smoked before the laboratory attendance) had little effect; the mean CO level of the LT smokers remained lower, but not significantly so.

The *rise* in expired-air CO concentration over the smoking of a single cigarette was significantly smaller for LT smokers than for the MT group, although the difference between groups was again less marked than the difference in standard CO yields (Table III).

Table III. Mean (± SD) expired-air CO concentration in MT and LT smokers (p.p.m.)

Tar group	*Standard CO delivery* (mg)	*Pre-smoking*	*Rise over smoking*
Middle	18.2	35.0 ± 18.4	12.5 ± 4.8
Low	11.7	30.2 ± 16.5	9.2 ± 4.3
		$t = 1.2$, NS	$t = 3.1$ $P < 0.01$
$\frac{\text{Low}}{\text{Middle}}$ %	64	86	74

Intensity of smoking and the estimation of relative nicotine and tar exposure

Given a cigarette of a particular standard delivery, the smoker's actual 'dose' of smoke constituents depends both on the amount of smoke produced and on the extent to which that smoke is inhaled. The term 'smoking intensity' is sometimes used to refer simply to those aspects of smoking behaviour which determine the amount of smoke generated from the cigarette (ie. the 'mouth-level exposure'). Thus a smoker taking frequent large puffs is said to smoke more intensively than one taking few puffs of small volume. However, a measure of smoking intensity which relates the actual *intake* of a smoke constituent to the standard delivery of the cigarette embraces both those aspects of smoking behaviour which generate smoke and those aspects (the depth and duration of inhalation) which determine the extent to which a smoke constituent is absorbed.

In the present study a measure of smoking intensity (in the latter sense) was obtained by dividing each smoker's CO level by the standard machine yield of the brand smoked. This gives a smoking intensity index expressed as expired-air CO concentration (in p.p.m.) per milligram of standard CO delivery. Using this measure, it appears that the LT group on average smoked their cigarettes more intensively than MT smokers (Table IV). When the index is based on pre-smoking levels the difference between groups is marginally significant. The difference is fully significant when the rise in CO over the smoking of the laboratory cigarette is considered. Since the pre-smoking concentrations reflect intake from a relatively long period of smoking in subjects' natural environment, the smoking intensity index used to estimate the relative nicotine and tar exposure of the two groups is based on pre-smoking values.

Table IV. Mean (± SD) smoking intensity in MT and LT groups (expired-air CO per mg standard CO delivery)

Tar group	$\frac{\textit{Pre-smoking CO*}}{\textit{Standard CO delivery}}$ %	$\frac{\textit{Rise in CO}}{\textit{Standard delivery}}$ %
Middle	31.0 ± 24.1	68.5 ± 25.9
Low	41.9 ± 34.9	83.3 ± 40.8
	$t = 1.6, P < 0.1$	$t = 1.9, P < 0.05$

d.f. = 75; 1-tailed test.
* Adjusted for number of cigarettes smoked.

Table V. Estimating nicotine and tar exposure

Nicotine

Tar group	*Smoking intensity index*	*Standard nicotine delivery* (mg)	*Nicotine intake* (arbitrary units)
Middle	31.0	1.52	47
Low	41.9	0.86	36
$\frac{\text{Low}}{\text{Middle}}$ %		57	76

Tar

Tar group	*Smoking intensity index*	*Standard tar delivery* (mg)	*Tar intake* (arbitrary units)
Middle	31.0	18.4	570
Low	41.9	9.36	392
$\frac{\text{Low}}{\text{Middle}}$ %		51	69

Table V shows the way nicotine and tar exposure were estimated. In both MT and LT groups, standard delivery multiplied by the smoking intensity index provides an estimate (in arbitrary units) of exposure. In the case of nicotine, the estimated exposure of LT smokers is 76% that of MT smokers; in the case of tar, 69%. Thus the intake of nicotine and tar by LT smokers is likely to be less than that of MT smokers, although it is unlikely to be reduced to the extent suggested by standard machine-smoked yields.

This use of a CO-based index to estimate exposure to nicotine and tar should be treated with some caution since the gas and particulate phases of cigarette smoke are likely to differ with respect to their distribution and absorption in the lung. Nevertheless, an index of smoking intensity based on CO has been found to match very closely one based on the actual measurement of nicotine (Ashton et al. 1981). Since no measure is available, the degree of association between tar intake and CO exposure has not been tested. However, since tar and nicotine are closely allied in cigarette smoke, it is likely that tar exposure may also be estimated using a CO-based index.

Discussion

Despite evidence of some compensation for reduced delivery, the present study supports the view that LT smokers are likely to be less exposed than their MT peers to harmful smoke constituents. This conclusion is in agreement with that of Wald et al. (1980) and Rawbone et al. (1978), but contrasts with the results of Russell et al. (1980) whose evidence showed that exposure to CO and nicotine was largely independent of the standard delivery of the brand smoked. The reason for this probably lies in the sample of smokers Russell et al. investigated. On average, the LT smokers in the Maudsley smoking-clinic group consumed twice as many cigarettes per day as in our own study. This suggests a heavier dependence on nicotine than is usual, and might account for the virtually complete compensation for the lower nicotine yields of the LT brands. The smokers may also have been especially eager to obtain a pharmacologically significant dose of nicotine in the stressful circumstances of having to provide a venous blood sample. But even in the study of Russell et al., it should be noted that LT smokers were likely to be less exposed to tar. As Rawbone (1980) has pointed out, the tar to nicotine ratios of LT and MT cigarettes are different, LT cigarettes providing a greater delivery of nicotine per unit of tar. Thus, even though their intake of nicotine was not appreciably less, the LT group would have had an intake of tar only 73% that of MT smokers in the case of men, and 80% in the case of women.

The similarity between the results of the present study and those of Wald et al. (1980) is striking. Wald et al. obtained an 'inhaling index'* for smokers of ventilated (i.e. LT) cigarettes which was 34% higher than that found for smokers of unventilated (i.e. MT) brands. In the current study, the corresponding smoking intensity index was 35% higher in LT smokers. When the 'inhalation' indices obtained by Wald et al. are applied to the standard yields of the brands involved in the present study, the nicotine exposure of LT smokers is estimated as being 75% that of MT smokers, and their exposure to tar 68%. These figures correspond to the 76% and 69% obtained using our own index of smoking intensity.

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* Use of this term is somewhat misleading. In fact Wald et al. calculated their index in a way very similar to that used in the present study. It therefore takes into account any differences in the amount of smoke generated from the cigarette as well as any differences in the depth and duration of inhalation.

Acknowledgement

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Br. J. Dis. Chest (1982) *76*, 397

Short Communication

FIBREOPTIC BRONCHOSCOPY: EFFECT OF EXPERIENCE OF OPERATOR ON DIAGNOSTIC YIELD OF BRONCHIAL BIOPSY IN BRONCHIAL CARCINOMA

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Summary

The results of biopsies of tumour seen during 144 fibreoptic bronchoscopies, performed by five operators, were reviewed to investigate the effect of experience with the procedure on diagnostic yield. 60.4% of a total of 490 biopsies showed carcinoma. At least one positive biopsy was obtained in 77.1% of cases. The modal number of biopsies taken per case by each operator was three. The diagnostic yield increased with the previous bronchoscopic experience of the operator ($P < 0.001$).

Introduction

The reported frequencies of obtaining histological evidence of carcinoma when an endobronchial tumour is seen at fibreoptic bronchoscopy vary considerably: Gellert et al. (1982) obtained unequivocal histological evidence of carcinoma in 78.6% of cases with visible endobronchial tumours, whereas Macdonald (1975) reported a rate of 91%. This high positive biopsy rate was apparently achieved by bronchoscopists with little initial experience with the technique. Several years after the introduction of fibreoptic bronchoscopy at the London Chest Hospital we are in a position to compare positive biopsy rates achieved by five operators with different previous bronchoscopic experience to investigate the effect of experience on diagnostic yield.

Methods

The results of bronchial biopsies of visible tumour in 144 examinations carried out by five bronchoscopists of varied experience who performed a comparable number of examinations during the period 1978 to 1981 at the London Chest Hospital were reviewed. A diagnosis of bronchial carcinoma was eventually confirmed by histological or cytological evidence in most cases or by clinical and radiological features in a small minority. The fibreoptic bronchoscopies were performed transnasally under local anaesthetic. All biopsies were obtained with an Olympus cup forceps through an Olympus BFB3 fibreoptic bronchoscope and were fixed in formalin. Paraffin sections were stained with haematoxylin and eosin and for mucin as required. Histological sections were re-examined by a pathologist (GS). The total number of biopsies taken and the number of biopsies showing unequivocal evidence of carcinoma were determined for each case.

Statistical analysis

Results were analysed to identify a trend towards increasing biopsy success rates with increasing experience of the operator using a method for testing for trend in proportions described by Snedecor and Cochran (1980).

Results

Of a total of 490 biopsies taken from visible tumour 60.4% showed evidence of carcinoma. At least one biopsy showed carcinoma in 77.1% of bronchoscopies where tumour was seen.

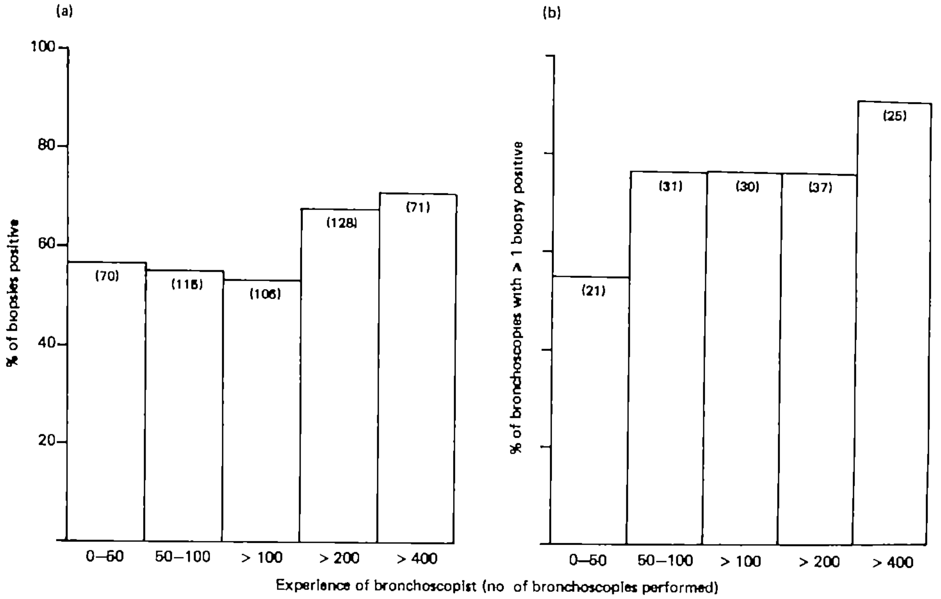

Fig. 1. (a) Relationship between proportion of biopsies that were positive and experience of the bronchoscopist. Figures in parentheses refer to total number of biopsies taken by each operator. (b) Relationship between frequency of obtaining at least one positive and the experience of the bronchoscopist. Figures in parentheses refer to the number of examinations carried out by each operator in this series of 144 patients

Fig. 1 (a) demonstrates the relationship between the proportion of total biopsies taken that showed evidence of carcinoma and the experience of the bronchoscopist. The positive biopsy rate increased with experience. There was a significant trend towards a higher frequency of positive biopsies with increasing operator experience ($P < 0.01$).

Fig. 1 (b) illustrates the relationship between the percentage of cases with visible tumour in which at least one positive biopsy was obtained and the experience of the bronchoscopist. There was a significant trend towards a higher frequency of obtaining at least one positive biopsy with increasing operator experience ($P < 0.001$).

The numbers of biopsies taken per case by each operator were not significantly different. The modal number of biopsies taken per case was three.

Discussion

We are not aware of any study comparing the diagnostic yields of bronchoscopists with varied previous experience.

Knight and Clarke (1979) noted an improvement in overall results as experience was gained at a single institution but no analysis of differences between operators was made.

We have found that bronchial biopsy performed by bronchoscopists with greater experience has a higher diagnostic yield. This factor may partly explain differences in positive rates reported in different series.

The modal number of biopsies taken per case in this series was three. We have previously shown that when five or more bronchial biopsies are taken from visible tumour, histological evidence of carcinoma is obtained in more than 95% of cases (Gellert et al. 1982), and we suggest that it may be possible for an operator to compensate for lack of experience by taking at least five biopsies from a visible tumour.

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Br. J. Dis. Chest (1982) *76*, 400

THE DERIVATION OF AN INDEX OF VENTILATORY FUNCTION FROM SPIROMETRIC RECORDINGS USING CANONICAL ANALYSIS

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Summary

An exploratory study was carried out to determine the optimum combination of indices read from a volume time curve to distinguish between individuals with respect to their ventilatory function. All subjects were without respiratory symptoms. The nine lung function indices read from the spirometric curve for each individual included FVC, FEV_1, flows over other segments of the curve and mean transit time. Applying a canonical analysis to the data, a combination of six indices was found sufficient to discriminate between individuals.

Introduction

The most widely used parameters obtained from expiratory spirograms are forced vital capacity (FVC), forced expiratory volume in three-quarters of a second ($FEV_{0.75}$), and forced expiratory volume in one second (FEV_1). In clinical practice and survey work many of the instruments used yield only these without obtaining the complete spirometric curve. While no formal way has been established of comparing complete curves, many attempts have been made to extract indices, such as mean transit time (MTT) (Fish et al. 1974), which describe more fully the shape of the curve or which relate more particularly to flows over the middle part of the curve. The latter are believed to be more closely related to early changes in the small airways than are $FEV_{0.75}$ or FEV_1 (Allen & Sabin 1971). In trying to describe lung function by a single index, much of the information given by the spirometric curve is discarded. If all the measurements read from a spirometric curve were considered simultaneously, several would be expected to be closely correlated with one another, resulting in duplications within the complete set of data. The study reported here is of an exploratory nature and it attempts to avoid these duplications by selecting a particular combination of indices to describe the ventilatory function of individuals.

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Methods

The 22 subjects (eight males and 14 females, age range 17–62) who participated in the study were drawn from the staff of the Medical College. All of the subjects were non- or ex-smokers and were free from respiratory symptoms. From each individual five expiratory spirometric curves were obtained on five successive days, using a McDermott spirometer (McDermott et al. 1968) modified in our workshop to give an electrical output signal from which the curves were produced as described by Derrett and Brown (1975). The nine indices read subsequently from the recordings were: FVC, FEV$_{0.75}$, FEV$_1$, FEV$_1$/FVC (%), peak flow (PF), maximal mid-expiratory flow (MMF) and mean transit time (MTT), together with the slope measurements S$_{5075}$ and S$_{7590}$ (see Fig. 1).

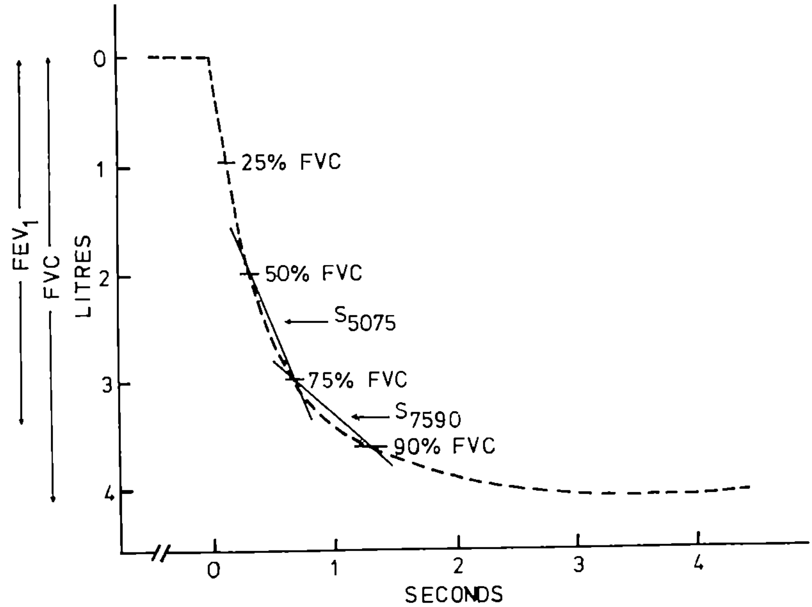

Fig. 1. Volume–time curve showing definition of S$_{5075}$ and S$_{7590}$

Peak flow (PF) is the maximum slope of the curve; MMF (the maximal mid-expiratory flow) is the forced vital capacity divided by twice the difference of the time at which 75% FVC has been exhaled and the time at which 25% FVC has been exhaled. The definition of MTT (mean transit time) is the area under the curve divided by the forced vital capacity. S$_{5075}$ is the slope on the curve between the points at which 50% FVC and 75% FVC respectively have been exhaled. S$_{7590}$ is the slope between the points at which 75% and 90% FVC respectively have been exhaled.

The objective was to determine how the lung function of individuals differed in a quantitative way using the technique of canonical analysis (Hope 1968; Morrison 1976). This procedure takes a linear combination of variables in a situation where there are too many variables to justify treating them singly. Consider p lung function measurements taken together then, because they are intercorrelated, it may be found that r of these measurements are superfluous, $p - r$ of them contributing all the relevant information.

The value of canonical analysis is that it enables one to study the relationship between groups of variables. In this experiment the repeated blows formed a group for each individual. If each blow is plotted for three variables, the resultant groups which these blows form will be roughly ellipsoidal. By obtaining a combination of the variables, the ellipsoids are transformed into spheres (points in three-dimensional space). Thus the information about each subject (that is the number of blows each person makes) is represented by a single point, the grouping of these points being roughly ellipsoidal. The canonical analysis then selects the major axis of the ellipsoid (that is the direction in which the scatter is greatest). A second axis, at right angles to the first, is selected so that it is inclined in the direction of the next greatest scatter. The direction given by the third and final axis is at right angles to both the first and second directions.

Results

In Table I a comparison is made of between- and within-subject variation from one measurement to another by calculating the components of variance which express variation between and within subjects as percentages of the total variation (Armitage 1971). The small within-subject component of variation for each of the measurements indicated the consistency of the five blows made by each subject. The correlation coefficients between and within subjects are shown in Table II.

Table I. Components of variance (expressed as percentages)

	$FEV_{0.75}$	FEV_1	FVC	$\frac{FEV_1}{FVC}$ %	MMF	PF	MTT	S_{5075}	S_{7590}
Between subjects	99	99	99	94	97	95	95	96	97
Within subjects	1	1	1	6	3	5	5	4	3

The importance of each measurement was assessed by a stepwise process, starting with all nine indices and at each step omitting the measurement which contributed least in accounting for overall variation. The first step was to examine the variation accounted for by all possible combinations of eight out of the nine variables. Since the combination which omitted $FEV_{0.75}$ resulted in the smallest decrease in overall variation, this variable was dropped and the process repeated taking all possible combinations of seven variables. On this basis MMF was the second variable to be omitted followed by S_{5075}. It appeared that six variables were necessary to describe the variation between individuals, namely: FEV_1, FVC, FEV_1/FVC (%), PF, MTT and S_{7590}. These variables accounted for over 96% of the total variation in the original nine variables.

Discussion

A combination of indices might produce the best description of an individual's lung function since information can be lost by trying to select the best single index. On the other hand, multiple indices read from the spirometric curve are intercorrelated both between and within subjects which results in overlapping

Table II. Correlation coefficients

Between subjects

$FEV_{0.75}$	FEV_1	FVC	$\frac{FEV_1}{FVC}$ %	MMF	PF	MTT	S_{5075}	S_{7590}	
1	0.998	0.93	0.218	0.815	0.831	−0.22	−0.728	−0.5	$FEV_{0.75}$
	1	0.939	0.192	0.799	0.816	−0.198	−0.712	−0.501	FEV_1
		1	−0.148	0.548	0.82	0.134	−0.435	−0.206	FVC
			1	0.721	0.038	−0.98	−0.798	−0.81	$\frac{FEV_1}{FVC}$ %
				1	0.587	−0.707	−0.983	−0.828	MMF
					1	−0.029	−0.457	−0.2	PF
						1	0.785	0.809	MTT
							1	0.879	S_{5075}
								1	S_{7590}

	$FEV_{0.75}$	FEV_1	FVC	$\frac{FEV_1}{FVC}$ %	MMF	PF	MTT	S_{5075}	S_{7590}
$FEV_{0.75}$	1								
FEV_1	0.946	1							
FVC	0.538	0.644	1						
$\frac{FEV_1}{FVC}$ %	0.427	0.355	−0.381	1					
MMF	0.719	0.611	−0.107	0.757	1				
PF	0.439	0.323	0.001	0.37	0.436	1			
MTT	−0.334	−0.25	0.438	−0.682	−0.659	−0.413	1		
S_{5075}	−0.643	−0.578	0.097	−0.748	−0.916	−0.23	0.563	1	
S_{7590}	−0.388	−0.39	0.248	−0.703	−0.629	−0.211	0.588	0.64	1

Within subjects

information. Since canonical analysis gives uncorrelated variates this duplication can be avoided. In the analysis described above, the reason for $FEV_{0.75}$ being excluded first was no doubt because FEV_1 was also included in the set of data. These two indices had the highest correlation both between and within subjects as can be seen from Table II. High correlation would be expected as both were forced expiratory volume measurements made over the same part of the curve.

In general, enough variables should be retained to account for at least 90–95% of the variation accounted for by all of the original variables. If 95% is taken to be a suitable point at which to stop, then six variables were found to be adequate, accounting for 96.3% of the 'explainable' variance. Using the 90% level as a 'stopping point', four variables: FVC, PF, MTT, and S_{7590} would adequately describe the variation, a result which corresponds very closely with the findings of McDonald and Cole (1980) whose analysis of indices read from a flow–volume curve suggested that 'there may be just four features of the flow–volume curve that can be used to discriminate between normal individuals'.

Unfortunately, it cannot be assumed that the variation in spirometry between normal subjects (due to differences in anatomical and physiological features) is the same as found with disease. It would therefore be interesting to carry out a similar study amongst subjects suffering from asthma and bronchitis to see whether the combination of lung function measurements which appeared to best describe the variation amongst the normal subjects in this study is also best for those with impaired lung function.

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BOOK REVIEWS

Respiratory Medicine and Intensive Care for the House Officer

John J. Marini

Baltimore/London: Williams and Wilkins. 1981. 1st edition. Pp. x + 273. Price $9.95

This is one of a series of manuals for the House Officer published from America, which just fails to fit in the English, though possibly not the Texan, pocket. The print has been produced directly from the typescript, and as a result there is some loss of clarity, which might lead to some difficulties if the book were referred to in the heat of the moment in a dim light. However, this method of production has enabled the book to be right up to date and to be produced at a reasonable price ($9.95).

The book is both American in style and in terminology. To take two practical examples, the colour coding of gas cylinders and the names and range of drugs available for emergency treatment of asthma are strictly for the United States.

In the preface the author emphasizes the need for the analysis of each case individually, and using general principles and guidelines rather than 'the cook-book approach'. To the English reader he still produces an over elaborate 'work-up' without clearly discussing the potential return from each course of action. The text could be shortened and clarified by keeping more closely to the relatively narrow remit of a manual for a House Officer. On the one hand insufficient knowledge is assumed, a dictionary definition of trocar and cannula is felt necessary, and on the other the discussion sometimes ranges wider than would be of immediate interest to the busy House Officer. For example, the prophylaxis of turberculosis is discussed in some detail. There is no bibliography. A short list of well chosen references would have enabled the author to have referred to matters of peripheral interest without discussing them in detail, and enable him to justify some of the more dogmatic statements, for example, that if pneumonectomy is to be considered, the critical FEV_1 is 800 ml, and the critical pulmonary artery pressure of the contralateral lung is 35 mm of mercury.

I was disappointed that the discussion of the management of acute pulmonary embolism was largely that of thrombolytic therapy, and not of the acute circulatory crisis. His handling of corticosteroids after an acute attack of asthma was not in accord with mine, and there were minor differences of detail between us in the management of acute crises, but otherwise I was sympathetic to the author's approach.

The book is necessarily too American in the practicalities to be of value to the British House Officer as a *vade mecum* during his time on the acute respiratory wards. Nevertheless, it is an enthusiastic and dynamic text which gives an interesting insight into the philosophy and approach of the management of acute respiratory problems on the other side of the Atlantic.

C. K. Connolly

Current Pulmonology 3

Daniel H. Simmons (editor)

Chichester: John Wiley & Sons. 1981. 1st edition. Pp. x + 441. Price £35

I found the title of this book ungainly and I doubt if the word 'pulmonology' is attractive to many British readers. Those who are not put off will find it a useful book which is the third of a series of annual reviews of respiratory disease. Twelve topics are covered, each with a different author or group of authors. Where as many as 21 authors are involved there is bound to be some variation in the standard and style of the sections but this variation is greater than might be expected. Some chapters have obviously been very well researched, are suitably critical in their appraisal of the subject and contain excellent summaries of the current state of thought and practice, whilst others fall short of this.

I can particularly recommend the chapter on obstructive lung disease by Richard Brashear in which he concentrates mainly on the mechanism of pulmonary hypertension and gives lucid descriptions of the experiments on which the current views of pathogenesis are based. Tuberculosis by John Sbarbaro is well worth reading and contains a helpful update on chemotherapy. Sonia Buist evaluates the tests of small airway function and for those who do not regard themselves as physiologists (and perhaps for some who do?) there is a most useful survey of the development of the various tests which are described in some detail and she gives a critical analysis of them. All respiratory physicians will learn a lot from the chapters on hypersensitivity lung disease, occupational lung disease and interstitial lung disease and the overlap between them enhances, rather than detracts from their value. The adult respiratory distress syndrome section includes much of the recent research regarding pathogenesis, but since there is still a good deal of uncertainty about this syndrome it is unfortunate that the authors do not clearly define the condition that they are discussing.

Lung cancer differs from the others because it seemed to be a standard textbook chapter and also very disappointing was the chapter on pulmonary rehabilitation. It is a very uncritical review but it is followed by a very full list of references, and those with a developing interest in the subject may find these of value.

A number of other books containing reviews and recent advances in respiratory medicine have been published in the last two years, and to some extent this is in competition with them, but this is a very nicely presented book and all physicians will find much in it to interest and inform them.

Roger White

Smoking; Psychology and Pharmacology

H. Ashton and R. Stepney

London: Tavistock Publications. 1982. Pp. 222. Price £9.95

This book is one of the most useful publications on smoking since the first RCP report. The pusillanimous manoeuvres of successive governments culminating in the recent failure of present Ministers even to develop the lines of advance promised by their predecessors have tended to make the opponents of smoking shrill in their frustration. Ashton and Stepney do not fail to indicate the immensity of the harm done to the British people by tobacco, though they still use a figure of at least 50 000 premature deaths when Wald and others have shown good reason for an estimate twice that size. They simply argue, as any reasonable and intelligent person should, that it must be our objective to reduce smoking as far and as fast as possible, to prevent its inception and to reduce, if possible, the harm that the residuum of smokers do to themselves. The book then analyses the psychological and pharmacological concomitants of smoking, which may lead the individual to start, cause him to increase to a level that is grossly harmful and make it difficult for him to stop.

This sort of background information is needed by anyone who has to advise smokers and help them if they are trying to give up. That group must include physicians with an interest in chest, including heart, disease and all general practitioners, community physicians and health educators. The book is mercifully free from the jargon of either of the professions of its authors and it will be readily intelligible to a non-professional readership too. Smokers are now a minority of less than two-fifths of the adult population in Britain. Some of them like the remaining majority of the population know perfectly well what the Government should, but will not do to help. Until Parliament finally addresses itself to its duty, there is still much in Ashton and Stepney's book which should help to maintain and further increase the reduction in cigarette sales achieved last year.

We do not need an elaborate theoretical basis for a policy of reducing smoking by any means we can — the epidemiological evidence is all too clear to anyone without a commercial interest. But an understanding of the subjective benefits the user seeks from nicotine and of the cunning way in which commercial promoters use them is useful. Nicotine dependence in the user is one of the salesman's assets and the development of smoking behaviour can be cleverly used in support. The self-regulation of nicotine intake and the probable consequence of a higher than anticipated intake of tar and carbon monoxide from supposedly less harmful cigarettes are well described. The exceptionally rapid absorption of nicotine during a puff is shown to be quite unlike delivery by any other route. Chapters on smoking as a psychological tool and smoking and personality are helpful to the physician and lead on to one on learning and breaking the habit. Less hazardous smoking – a description the salesmen try hard to convert into 'safe' smoking – is a collateral objective of the main health programme, that of diminishing smoking by any persuasion open to us. The last five pages on 'future prospects' end with the comment: 'Nevertheless the attempt actually to reduce the risk of smoking is beset with difficulties. In addition to the uncertainties already described the very concept of safer smoking may discourage people from the only truly safe course of action which is either never to start smoking, or, if started, to stop.' This book will be a great help to the vast majority of health workers whose objective is contained in those last nine words.

G. E. Godber

Pathophysiology of Respiration

Meir H. Kryger (editor)

New York: John Wiley & Sons. 1981. 1st edition. Pp. xvi + 352. Price £12.95

This book is written by numbers of Departments of Medicine and Paediatrics in the Universities of Manitoba and British Columbia, with a chapter from Thomas L. Petty of the University of Colorado. Meir Kryger edited it and wrote eight of the 17 sections. It is a very good book indeed.

The important problems (airflow obstruction, immunological lung disease and asthma, respiratory failure, and hypoxia, for example) are fully discussed and the whole book is illustrated by admirable line diagrams. Looking for topics which are frequently ignored or badly handled, we find excellent sections on adult respiratory distress syndrome, lung defences, the pleural space, and altitude. For acid–base diagram they use a $P\mathrm{CO}_2$–bicarbonate diagram, thus elegantly avoiding the great pH–hydrion debate.

Any reviewer will have minor reservations about detail, and one has to put a few in to show one has read the book. I thought it was a pity not to mention convective acceleration on pp. 15–16, or stress the point that driving pressure from alveolus to equal pressure point is equivalent to lung elastic recoil pressure. The reason why PEEP decreases cardiac output is much argued, and the explanation given here is inadequate. I would like a more detailed account of the indications and effects of long term oxygen therapy in patients with chronic airflow obstruction, which leads me to a difficulty with all books on pathophysiology, namely how much therapeutics to put in. Thus there is an extensive account of drugs used in treating asthma, very reasonably, but for carcinoma of the bronchus there is the briefest note about operability, the statement that chemotherapy cannot as yet cure but nothing further, and no mention of radiotherapy. I don't know the answer to this problem and it doesn't detract from the overall high quality of the book.

I hope it succeeds as it deserves to with undergraduates, respiratory physicians at the outset of their training, and their teachers.

K. B. Saunders

Exercise in Health and Disease

Francis J. Nagle and Henry J. Montoye (editors)

Springfield, Illinois: Charles C. Thomas. 1981. 1st edition. Pp. xiv + 326. Price $31.50

This title may attract many interested in exercise physiology and the text, according to the fly-leaf, will be 'invaluable to physicians, physical therapists and physical education specialists'. However, beware. This book consists of the proceedings of a symposium held in 1979, and is not a textbook. As is the case with many symposia, no attempt is made to cover the subject comprehensively. Topics dealt with range from the muscle mitochondrion to the psyche, from the paediatric to the geriatric, from sea level to high altitude. Many contributions are inconclusive, anecdotal or incomplete ('results will be available in mid-1980'). Occasionally there are ethical queries: how many committees would sanction thigh muscle needle biopsies in 13 normal six-year-olds? In places the text is in pseudoscientific American – an increasingly indigestible language for the simple Briton. The reader grapples with statements such as 'self motivation is conceptually a trait-like behavioural disposition that is situationally invariant' and 'an accurate perception of physical exercise suggests the possibility of a conflict-free area of ego functioning related directly to physiological stimuli which is uncontaminated by cognitive disturbance'.

There is some interesting speculation on limiting factors in aerobic capacity and on the development of fatigue, but this information is greatly diluted by the more lightweight contributions. One is left in the hope that the worthwhile scientific content will transcend these pages and find a more succinct and enduring forum.

Clive McGavin

Aerosols, Airways and Asthma

Joseph J. Trautlein (editor)

Lancaster: MTP Press Limited. 1981. 1st edition. Pp. x + 102. Price £11.95

The foreword to this book states that 'we resist the temptation to take a vantage point from the ionosphere' – good news perhaps but a foretaste of the density of the prose elsewhere in this curious book. The eight chapters on assorted aspects of aerosols and asthma, ranging from 'Basidiomyecetes as aeroallergens' to 'Philosophy of therapy' are neither comprehensive nor obviously linked. Although not stated, I assume that the book arose from a meeting. There are few references after 1975.

The format varies; one detailed personal study of human exposure to aerosol propellants contains 18 pages of undigested raw data, one picture of the subjects looking like an end of term school photograph, and several pictures of apparatus such as man blowing into polythene bag and a piece of paper with numbers on. Most chapters adopt more of a review format but these tend to be bland and are not necessarily helpful. The chapter on pulmonary function tests mentions 15 or 20 tests which can be done in asthma, such as frequency dependence of compliance and closing volume, but omits regular peak flow measurements. Elsewhere we are told that asthma may be due to beta-adrenergic blockade, cholinergic imbalance or that the alpha-adrenergic system may be involved. It may be due to a hundred and one causes but without a more critical appraisal the reader is none the wiser.

A. E. Tattersfield

Practical Fibreoptic Bronchoscopy

Kenkichi Oho and Ryuta Amemiya

Tokyo: Igaku-Shoin. 1980. Pp. xii + 112. Price $31.50

This book unashamedly advocates the flexible instrument for all indications, furthering the futile controversy of rigid versus fibreoptic bronchoscopy that we have all become so tired of. The authors do seem to have had wide experience of massive haemorrhage and some of foreign body removal—problems perhaps sometimes were safely removed by rigid bronchoscopic techniques. In parts it reads like promotional material for a well-known brand and exalts passage of the instrument throught the mouth after complicated local anaesthetic procedures. This method is favoured by few only in the United Kingdom, others preferring the nasal approach to insertion. Thus the book provides a rather limited account of the procedure where it could have discussed a more comprehensive usage of this extremely versatile instrument.

The authors rightly view the procedure as safe in a wide variety of conditions but the few dangers of, for example, bronchoscopy in the presence of severe respiratory failure, haemorrhage from biopsy of 'non-malignant' tumours and pneumothorax during transbronchial lung biopsy are understated or not mentioned at all. Most operators would disagree with the authors that a bleeding time is desirable before all bronchial biopsies and that transbronchial biopsy is always contraindicated in bleeding disorders.

The detailed chapter on accessory instruments available for 'Brand X' is helpful with clear photographs, whilst the chapter on cleaning and sterilization of instruments gives a thorough and useful account of bronchoscopic care. Easy and routine bronchial toilet with the fibreoscope is described and rightly emphasized. No practical manual on the subject would be complete without an atlas of bronchial anatomy and the photographs here are clear and fully annotated. The very numerous views of endobronchial carcinomas are satisfactory but repetitive and the claim that the gross appearance of tumours is an aid to guessing the histological type is, in my view, false.

There are some omissions of note, the most important of which are: absence of practical hints for the learner, failure to recognize the possible difficulties of interpretation of histological appearances of small fibreoptic biopsy specimens, failure to discuss the relative values of other (non-fibreoptic) biopsy techniques and lack of mention of the possible value of bronchial lavage, a subject which had been more than hinted at when this book went to press.

This is a limited book which describes the indications, instruments and methods used by the authors and can only be recommended to those who wish to follow them.

D. E. Stableforth

Cancer Treatment and Research I. Lung Cancer 1

R. B. Livingston

The Hague: Martinus Nijhoff. 1980. Pp. xiv + 310. Price DFl 90

This volume is the first of a series to provide authoritative reviews on current treatments and research into major oncological topics. It aims to review advances in several areas of the management of lung cancer: radiotherapy, especially for non-small-cell tumours; small-cell cancer (pathology, staging and treatment); the results of immunotherapy and carcinogenesis. The sequence of chapters is in the main logical, beginning with 'pulmonary carcinogenesis': aryl hydrocarbon hydroxylase (AHH). This chapter is made harder to digest by the intense referencing within the text (193) and the problems of differentiating hypothesis from fact in the possible value of AHH as a biochemical marker to identify individuals at risk of developing lung cancer.

The next two chapters on immunotherapy, one as an adjuvant to surgery and the other more general, contain much repetitive review data. McGuire's section on adjuvant immunotherapy concludes that 'immunological stimulation has ... no proven efficacy over surgery alone', whilst Holmes states from much the same data 'there have been few entirely negative studies'! These conclusions highlight a dilemma that runs throughout the book. Whilst all chapters contain excellent thorough reviews of their subject matter, most lack an overview to state critically which data are acceptable and, more important, which aspects still remain to be studied or re-evaluated in the future. The glaring lack of controlled studies in many important treatments of lung cancer is glossed over. In the chapter on post-resection irradiation by Green the results of two large studies, although suggestive that irradiation to the mediastinum prolongs survival, are taken as sufficient reason to justify this therapy, but should instead set the stage for careful prospective controlled studies. Similarly White and Boles, discussing radiotherapy in inoperable limited disease non-small-cell lung cancer, also fail to state the need for controlled prospective studies. Their chapter also contains unnecessary radiotherapeutic technicalities but does discuss the potential value of computed tomography in field planning. More than half the book is devoted to radiotherapy, including a long chapter on new approaches for radiotherapy including hyperbaric oxygen, hypoxic cell sensitizers and hemibody irradiation. Although these may be potentially useful additions to treatment there are insufficient clinical data available to justify 73 pages.

Small-cell lung cancer is comprehensively reviewed—a short chapter on staging, then a review of therapeutic results which disappoints in its very short and rather barren forward look. The book's last chapter, on the pathology of small-cell tumours, is peculiarly out of sequence and would better preface the chapter on treatment as it contains new and interesting data by Matthews on the effect of subtyping small-cell cancer and how this affects responses to therapy and survival—some of the most interesting data in the book.

Strangely in a book on treatment there is no chapter on surgery. Although surgical results are discussed, surgery remains the best chance of cure in non-small-cell lung cancer and a surgical view, possibly evaluating mediastinoscopy, CT scanning and other refinements of preoperative staging, would have been appropriate.

In all, this book contains a fund of well presented easily readable information bringing the reader up to date. It could, however, have been more critical of those often-quoted key but uncontrolled studies that so much is still based on today.

Stephen G. Spiro

Respiratory Physiology III; International Reviews of Physiology 23

J. G. Widdicombe

Baltimore: University Park Press (Lancaster: MTP Press). 1981. Pp. xii+339. Price £17.75

For the clinician with an interest in respiratory physiology, or the physiologist deciding to explore new territory, this new edition provides an excellent and up-to-date review of six fields of growing interest in respiratory physiology. Each chapter is written by a recognized authority and provides extensive references.

I particularly enjoyed the chapter on exercise by Wasserman, Whipp and Davis. This must be one of the best reviews of the subject, extending from basic principles of cellular respiration to breathing control during exercise. J. E. Remmers' chapter on effects of sleep on control of breathing is also both topical and practical, offering a considerable guide to the interested clinician.

The same blend of practical and theoretical is to be found in the chapters on airway mucociliary system by R. J. Phipps and breathing before and after birth by B. S. Dawes and D. J. Henderson-Smart.

I was a little disappointed in the chapter on neurohumeral control of airway caliber, which is extensive and introduces the role of neuropeptides and SRS-A in airway control, but fails to include McFadden's observations on airway cooling in exercise-induced asthma. A survey of applications of modelling to respiration by E. S. Peterson provides an extremely well written and concise account of this important field to physiology. The style of writing and description allows easy comprehension even in the non-mathematician and invites further reading.

In short this book is a must for every scientific and clinical respiratory physiology laboratory.

Tim H.

Pulmonary Disease in the Adult

D. R. Gracey (editor)

Chicago: Year Book Medical Publishers Inc. 1981. 410 pages incl. index. Price £29.50

This is a concise account of the spectrum of diseases of lung, pleura, mediastinum and oesophagus that might be encountered in North America. Its 17 chapters are written by 21 specialists, mainly from the Mayo Medical School. Each chapter ends with a list of references, the most recent of which are dated 1978. The book is aimed at the primary care physician, rather than the thoracic specialist and deals with disease in the adult, particularly the 'older' adult.

The good points of this book are that it does cover many aspects of thoracic medicine succinctly. These include lung physiology, immune defence mechanisms, pulmonary manifestations of systematic disease and occupational lung diseases. The figures are clear, the X-rays reproduce reasonably well and there are macro- and microscopic illustrations in black and white of lung pathology.

On the negative side, it is aimed at a North American market, where inevitably terminology and practice are slightly different. The account of treatment for tuberculosis is at best, non-European, and at worst idiosyncratic. In the chapter on asthma, we are given an incomplete list of 50 diseases with which wheeze has been associated, including asbestosis and pleural neoplasms.

It is difficult to see who in Britain might want to buy this book in view of the choice of large and small British textbooks on chest disease. My copy will be left on the ward for the nurses and junior staff to refer to.

Clive McGavin

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